



PHD

Approaches to carbon analogues of ellipticine

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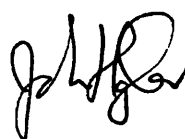
APPROACHES TO CARBON ANALOGUES OF ELLIPTICINE.

submitted by John David Hayler for the
degree of Ph.D. of the University of Bath
1988.

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SUMMARY.

This thesis discusses approaches towards the synthesis of 9-hydroxy-5,11-dimethyl-6*H*-pyrido[4,3-*b*]fluorene, the 6-carbon analogue of 9-hydroxyellipticine. The work is based on three main reactions.

The first uses the photochemical cyclisation of stilbenes to phenanthrenes. Attempts to prepare an appropriately functionalised pyridostilbene were unsuccessful, however, 6-methoxy-1,4-dimethylphenanthrene was prepared using this methodology and some reactions of this product were explored.

The second approach was based on the Diels - Alder reaction as a means of preparing fluorenes. 5-Methoxy-1-indenone was used as the dienophile and 3-substituted-2,5-dimethylfurans were used as the diene. The preparation of *t*-butyldimethylsilyloxymethyl-4a,9a-dihydro-6-methoxy-1,4-dimethyl-1,4-epoxy-9-fluorenone and attempts to aromatise this molecule are described.

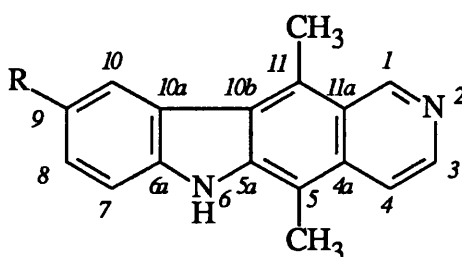
The third approach is based on the lithiation of 3-ethylpyridine for reaction with an appropriately protected 3-bromo-5-methoxy-1-indanone and the protection of this molecule is discussed.

Finally a return to the Diels - Alder methodology using *trans*-2-*trans*-4-hexadiene as the diene resulted in the preparation of 6-methoxy-1,4-dimethylfluorene. Selective chloromethylation and pyridine ring annulation using a Bischler - Napieralski cyclisation resulted in the preparation of the phenylsulphonyloxy- protected form of the target molecule.

1. INTRODUCTION.

1.1. Isolation and biological activity of the ellipticines.

The alkaloids ellipticine (1) (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) and 9-methoxyellipticine (2) were first isolated by Goodwin, Smith and Horning ¹ in 1959 from the leaves of *Ochrosia elliptica* Labill (family Apocynaceae) a tree which is native to tropical Asia, Oceania and many Pacific islands. These alkaloids and structurally related compounds have since been found in a number of other plants. ²⁻⁴

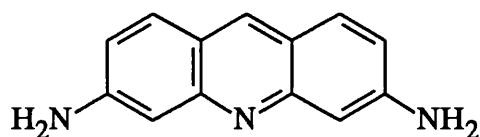


The structure of ellipticine was confirmed by Woodward ⁵ in 1959 by a total synthesis, but interest ⁶ in the alkaloids has been maintained since then because of the observation that ellipticine ⁷ and 9-methoxyellipticine ⁸ show activity against several experimental tumours in animals.

1.2. Current theories of the mode of action of the ellipticines.

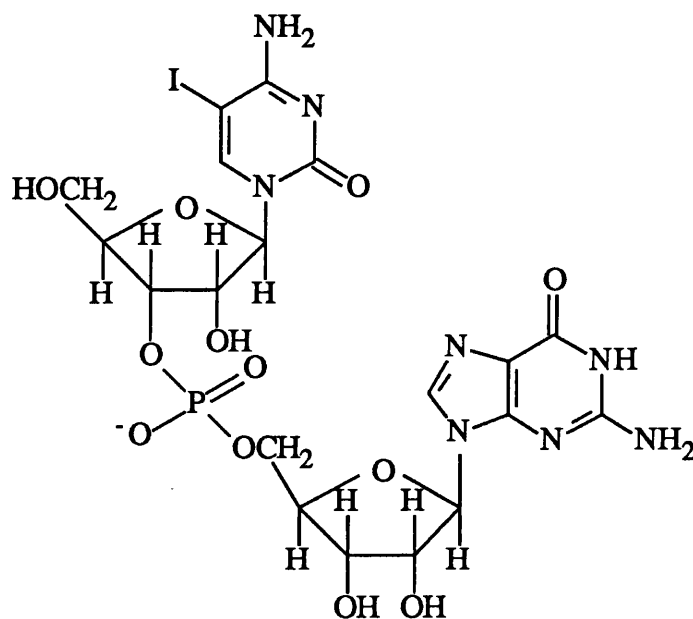
Despite this long history the anticancer mechanism of ellipticine and its derivatives is not clearly understood, although several hypotheses have been proposed based upon the large amount of work which has been done in this area. In 1975 Kohn *et al.* ⁹ showed that ellipticine caused an increase in the viscosity and a decrease in the sedimentation rate of native calf thymus DNA. The magnitude of these changes was found to be similar to that produced by proflavin (3), which is a known DNA inter -

calating agent, and therefore it was argued that ellipticine, also a planar molecule, exerted its effect by intercalation between the base pairs of DNA.



(3)

Furthermore, experiments with circular DNA showed that the binding of ellipticine to DNA resulted in a local unwinding of the double helix resulting in a change in the unwinding angle of 7.9° (proflavin = 8°). These results are in agreement with the changes expected from theoretical calculations ¹⁰ and provide overwhelming support for the previous conclusion. Finally an X ray structure analysis ¹¹ of the co-crystallisation product of ellipticine with 5-iodocytidylyl(3',5')guanosine(4) established that in this complex the alkaloid is stacked in between the hydrogen - bonded base pairs and its presence causes a distortion in the arrangement of the sugar - phosphate unit compared with that of the parent nucleotide.



(4)

More recent ^1H n.m.r. studies ¹² add further evidence that ellipticine intercalates into DNA, and Le Pecq and co - workers ¹³ have compared the DNA binding properties of various ellipticine derivatives in order to try and rationalise structure - activity relationships. Their results are shown in Table 1. The apparent binding constant, K_{AP} , was obtained by measuring the ability to compete with ethidium bromide (5) in binding the DNA.

THE DNA BINDING PROPERTIES OF SOME ELLIPTICINES.

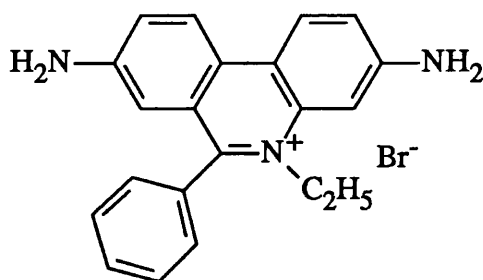
DERIVATIVE	K_{AP} (pH 7.4)	UNWINDING ANGLE	ACTIVITY ^c
6- <i>N</i> -isopentyl	1.0×10^4	8.8 ^a	0
6- <i>N</i> -isopentyl-9-methoxy	1.0×10^4	-	-
Nor-5,11-dimethyl	1.0×10^4	-	0
Nor-11-methyl	2.4×10^4	-	0
9-methoxy	1.0×10^5	6.8	90
Ellipticine	1.5×10^5	9.0	94
9-bromo	4.0×10^5	0.0 ^b	0
6- <i>N</i> -methyl	4.0×10^5	10.2	92
9-amino	1.2×10^6	4.0	0
6- <i>N</i> -methyl-9-methoxy	2.0×10^6	5.0	50
9-hydroxy	2.0×10^6	12.0	99.9

a) Measurement made at pH 5.0.

b) 9-bromoellipticine does not intercalate.

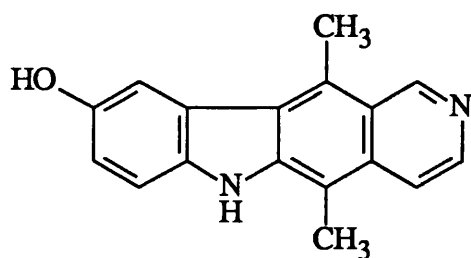
c) The pharmacological activity is expressed as the percentage of mouse L 1210 Leukemia cells killed by one third of the LD₅₀.

Table 1.

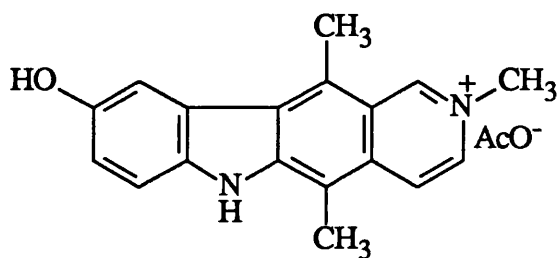


(5)

The most important feature of this work was that it highlighted the possible use of 9-hydroxyellipticine (6) as a drug. In fact this compound has since been shown to exhibit a very high activity against a number of human cancers, as well as a low toxicity at therapeutic dose. Indeed the quaternised form of this drug 9-hydroxy-*N*-2-methylellipticinium acetate (7) is marketed in France as “Celliptium” and is used clinically in the treatment of breast cancer.¹⁴



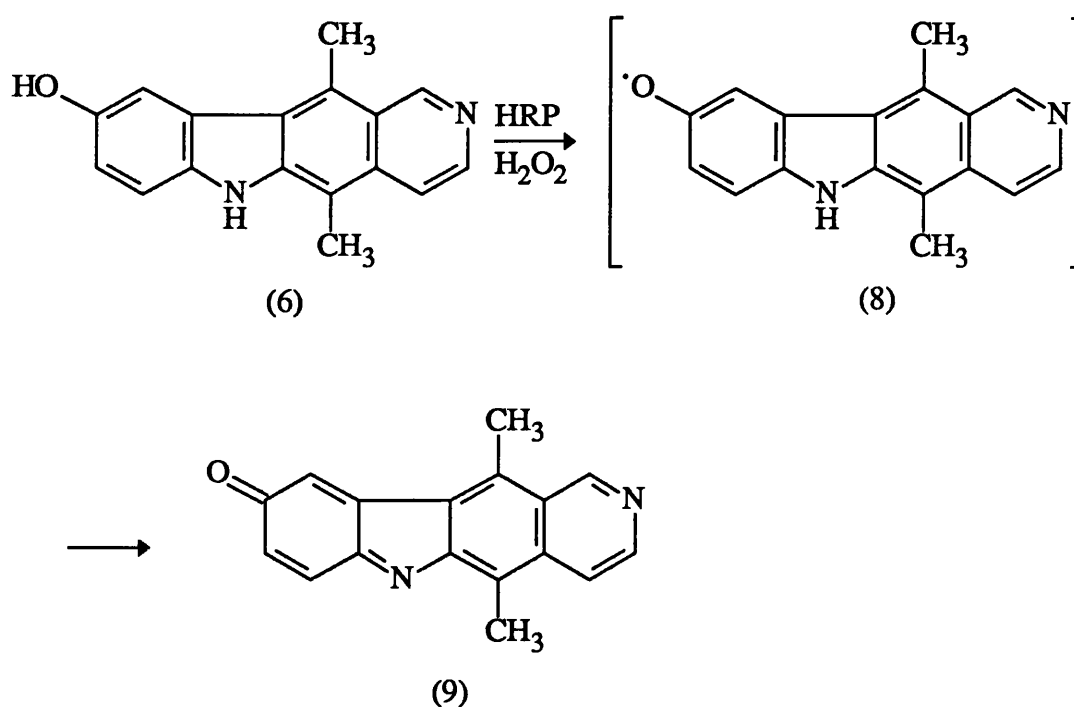
(6)



(7)

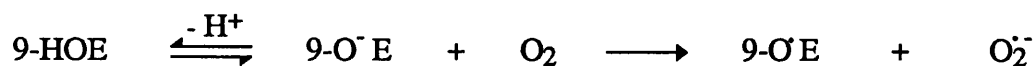
The known intercalation of ellipticine and its high binding affinity for DNA were at first considered as the reason for the antitumour properties exhibited. However, Le Pecq's work has shown that DNA binding affinity alone is not sufficient criteria for activity as 9-aminoellipticine binds more effectively than ellipticine itself and yet shows no activity. Thus it may be that there is an *in vivo* modification of the drug leading to enhanced activity and in support of this it has now been established that ellipticine is oxidised *in vivo* to both 9-hydroxyellipticine (major product) and 7-hydroxyellipticine

by a cytochrome *P*-450 mixed function oxygenase system.^{15,16} It is possible that the active form of the drug is 9-hydroxyellipticine and that this strengthens the intercalating complex by hydrogen bonding with the phosphate groups or bases in the DNA. This is reflected in the increased binding affinity of 9-hydroxyellipticine compared to ellipticine itself, (Table 1). Additionally *in vitro* experiments by Auclair and Paoletti¹⁷ show that 9-hydroxyellipticine, in the presence of horse-radish peroxidase (HRP) / hydrogen peroxide, undergoes a further two -electron oxidation to the iminoquinone (9) (scheme 1).

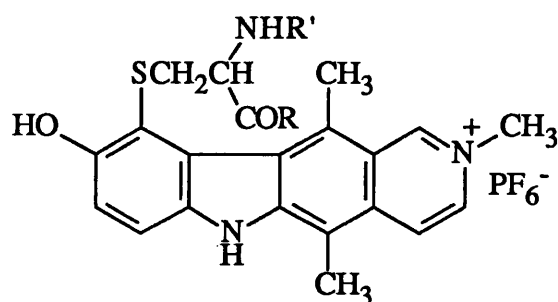
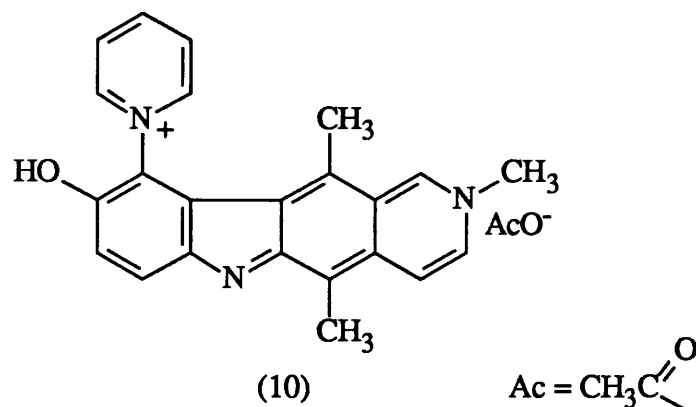


Scheme 1.

This oxidation is thought to proceed *via* the intermediate phenoxy radical (8) (detected by e.s.r. spectroscopy) which can then undergo further oxidation to the iminoquinone (9). It has been further proposed^{4,14} that the generation of these phenoxy radicals *in vivo* could be explained by the reduction of molecular oxygen to superoxide ions and that these superoxide ions could be responsible for the observed irreversible DNA strand breaks induced by ellipticines.^{18,30}



Further study ¹⁹ of the *in vitro* oxidation system has revealed that the iminoquinone (9) is regiospecifically alkylated at position 10. Thus pyridine affords the salt (10), while cysteine gives compound (11).

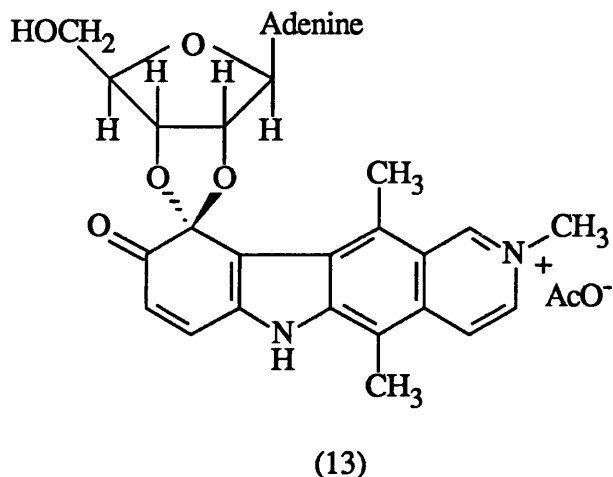


(11) R = OH, R' = H

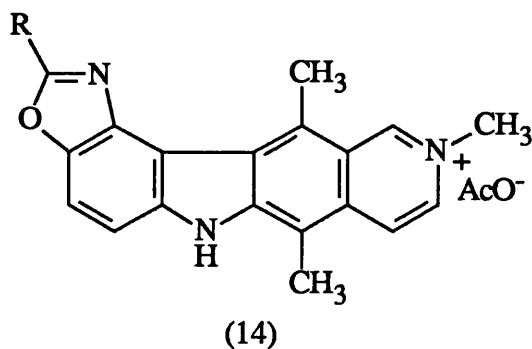
(12) R = NHCH₂COOH
 R' = COCH₂CH₂CH(NH₂)COOH

The possibility that a similar event occurs in the cell is supported by the isolation of the glutathione adduct (12) in the bile of rats treated with 9-hydroxyellipticine. ²⁰ The last adduct, together with the monoacetate of the cysteine compound (11, R = H, R' = OAc) have also been obtained from rat urine ²¹ and the cysteine adduct (11) is present in the urine of human patients after treatment with Celliptium. ²¹

The iminoquinone (9) has also been shown to react specifically with adenosine to yield the spiro derivative (13).^{22,23}



Similarly alkylation at C-10 of the iminoquinone with amino acids²⁴ affords oxazoles of the type (14).²⁵



R = H, Glycine adduct
R = CH₃, Alanine adduct

As a result of this and other work^{26,27} it has been suggested²⁶ that 9-hydroxy-*N*-methylellipticinium acetate may alkylate the terminal sugar residues of either transfer-RNA or messenger - RNA to inhibit protein biosynthesis. Furthermore the formation of oxazole adducts (14) by the reaction of amines with 9-hydroxyellipticine under oxidative conditions²⁸ has led to the proposal⁴ that iminoquinones generated *in vivo* could cross link to protein molecules, having free amino and thiol functionalities. As a

result ribonucleic acid polymerase could be inhibited.²⁹

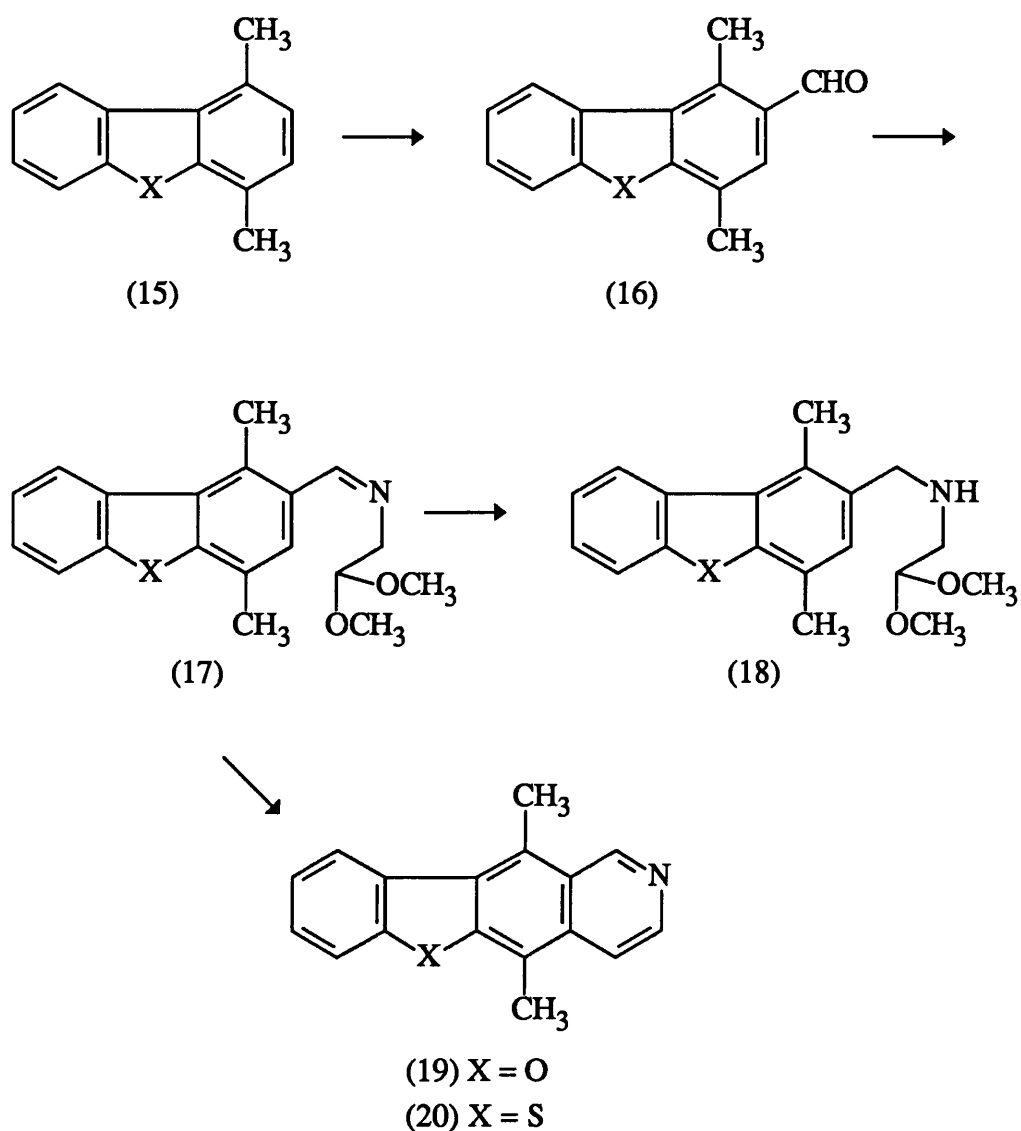
Ross *et al.* have demonstrated^{30,31} that ellipticine causes protein associated DNA strands to break. As a consequence they consider^{31,32} that the protein linked with the fragmentation process is an enzyme that recognises the DNA distortion at the intercalation site. This enzyme attempts to repair the damaged DNA by severing the DNA chain and binding the residue to itself *via* a phosphoryl terminus. This type of enzyme is known as a topoisomerase and more recent work by Tewey *et al.*³³ has established that mammalian topoisomerase II when treated with either ellipticine or 9-hydroxy-*N*-methylellipticinium acetate also causes protein linked strand breaks to occur. These workers propose that the drugs promote the formation of a cleavable complex of topoisomerase II and DNA and that, following work on other intercalating drugs, DNA topoisomerase II may be a common target for intercalating drugs.

Currently this area is of intense interest to biochemists but as yet their conclusions do not have the precision which is necessary to define new targets for chemists to synthesise. Hopefully this will soon change and the jargon associated with these important studies will become more meaningful to the organic chemist. At the moment, however, the only conclusions we can draw are (a) that ellipticine probably acts *in vivo* in a number of ways and (b) that the most potent drug in the series is 9-hydroxyellipticine.

Although this compound appears to be a useful drug, patients undergoing treatment with it suffer from a number of side effects including nausea, vomiting, hypertension, muscular cramps, fatigue, mouth dryness and mycosis of the tongue and oesophagus.¹⁴ Studies in mice³⁴ have also shown that the toxicity is cumulative and that problems of weight loss and hypothermia can be caused by doses as low as one fifth of the sublethal dose. These problems coupled with the poor solubility of ellipticine derivatives in aqueous media at physiological pH mean that there is still a need to find alternative structures which show similar activity to 9-hydroxyellipticine, but without its side effects.

1.3. Isosters of the ellipticines.

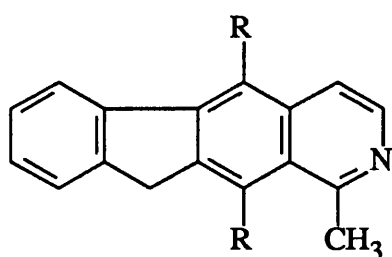
In the search for a more effective drug efforts have been made to synthesise ellipticine analogues which do not contain the indole nitrogen. As examples, preparations of oxa- and thia- ellipticines: 5,11-dimethylbenzofuro[2,3-*g*]isoquinoline (19) and 5,11-dimethylbenzothieno[2,3-*g*]isoquinoline (20) were reported simultaneously by Elmes and Swan ³⁵ and by Fujiwara, Acton and Goodman. ^{36,37} Both groups used a modification of Cranwell and Saxton's ellipticine synthesis, ³⁸ which embodies a Pomeranz - Fritsch cyclisation of the appropriate dihydroazomethine (18) (Scheme 2).



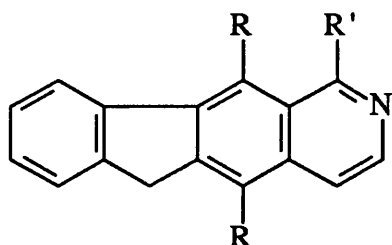
Scheme 2.

These authors claim, however, that it is unnecessary to reduce the azomethines (17, X = O or S) (*cf.* Dalton *et al.* ⁷) and a direct conversion into the fully aromatic products is achieved simply by treating these substances with “super” phosphoric acid. No detailed biological data were presented at the time and one must conclude that neither compound showed useful anticancer activity.

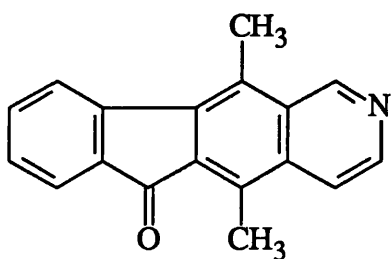
A number of pyridofluorenes (21 - 25) have also been synthesised by Dixit, Khanna and Anand ³⁹ using variations of the route illustrated below (Scheme 3) for the construction of 5,11-dimethyl-6*H*-pyrido[4,3-*b*]fluorene (24).



- (21) R = H
(22) R = CH₃

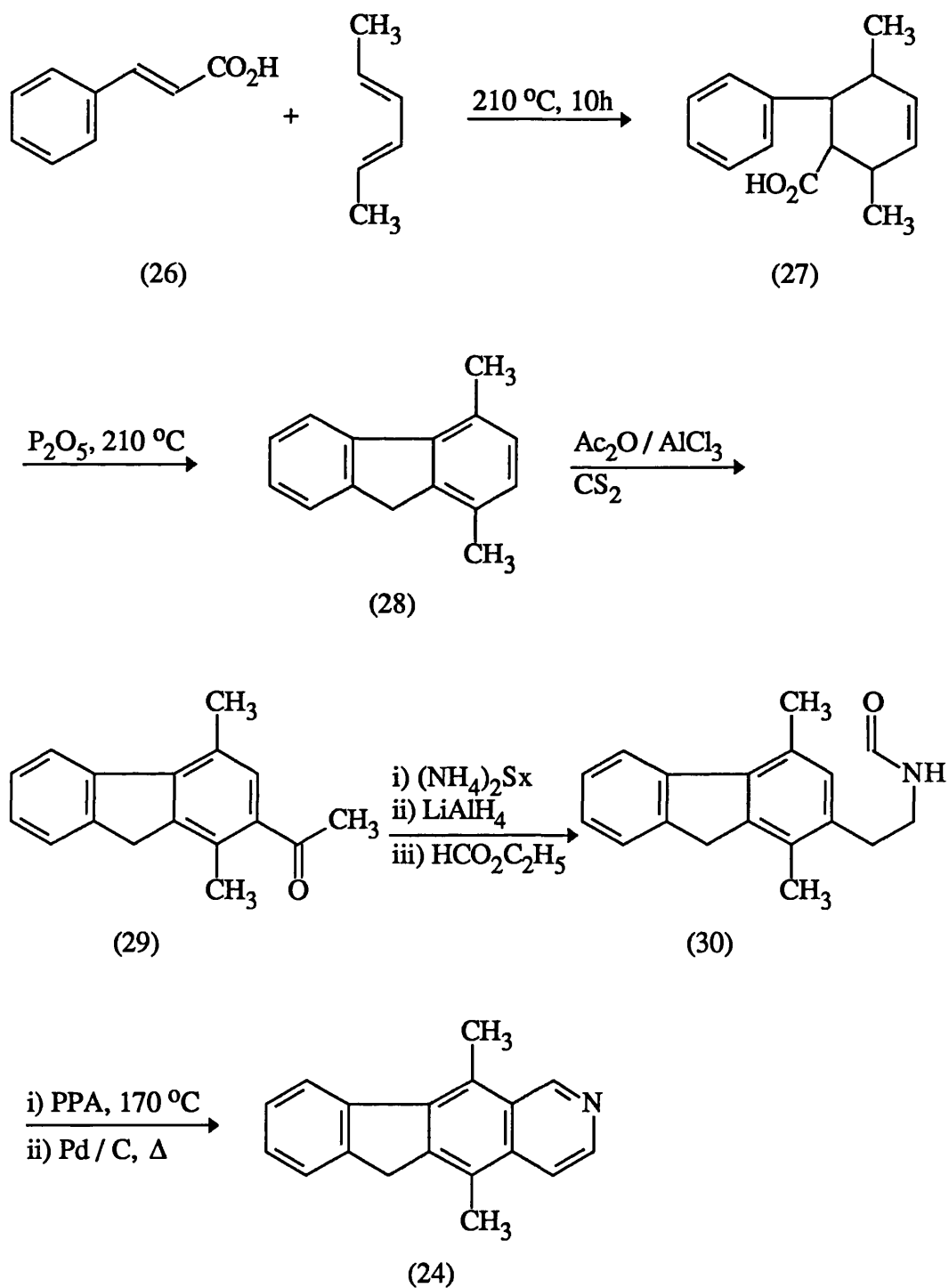


- (23) R = H, R' = CH₃
(24) R = CH₃, R' = H



(25)

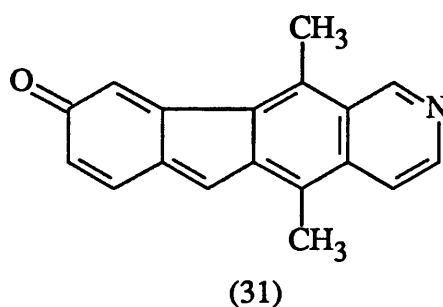
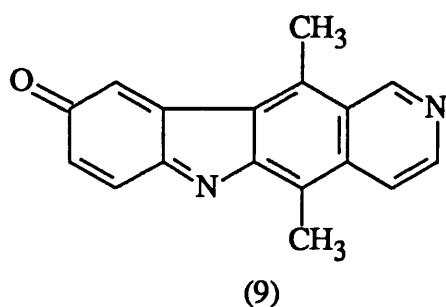
2-Acetylfluorene (29) was the common intermediate in the syntheses of all the analogues. None of the tetracyclic products showed any activity when screened for anticancer, antifungal or antibacterial activity. They were also reported not to react significantly with DNA.



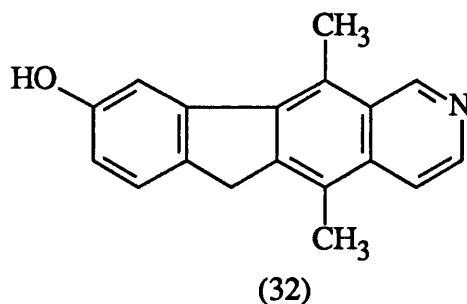
Scheme 3.

These findings prompted Dixit and his colleagues to comment “Therefore it seems that the indole ring is essential for the biological activity of ellipticine and related pyridocarbazoles.”

This could well be the case if an iminoquinone is the true drug in the ellipticine series, and it could be argued that the indolic nitrogen atom of ellipticine provides the necessary electronic activation which allows enzymic oxidation first to 9-hydroxy-ellipticine and thence to the “true” drug (9). When the -NH function is replaced by a methylene group this activational influence is missing and the oxidation potential of the benzenoid A-ring may be too high to permit hydroxylation and the ultimate production of quinonemethide (31) analogous to the iminoquinone (9).

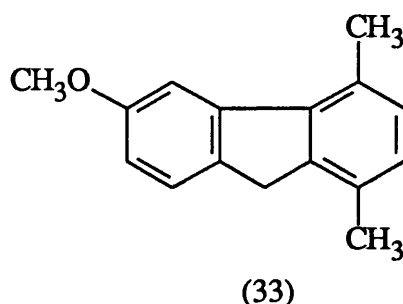


If this speculation is correct then any drug designed to act in the same manner as ellipticine, but which lacks the activational influence of the indolic nitrogen atom should have a hydroxyl substituent at C-9. To this end Sainsbury and Popplestone^{40,41} considered that 9-hydroxy-5,11-dimethyl-6H-pyrido[4,3-*b*]fluorene (32) should be made and tested for anticancer activity.

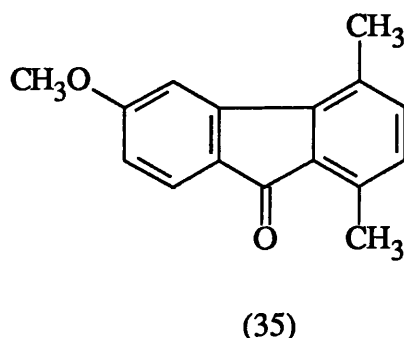
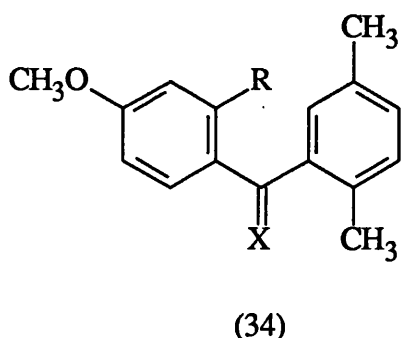


1.4. Approaches to 9-hydroxy-1,4-dimethyl-6H-pyrido[4,3-*b*]fluorene.

These authors attempted to synthesise this compound by a modification of Dixit's route to the parent compound, using 3-methoxycinnamic acid rather than cinnamic acid. However, despite many hours of effort, they were unable to achieve a Diels - Alder reaction between this compound and 2,4-hexadiene. In order to overcome this problem other routes to 6-methoxy-1,4-dimethylfluorene (33) were considered.



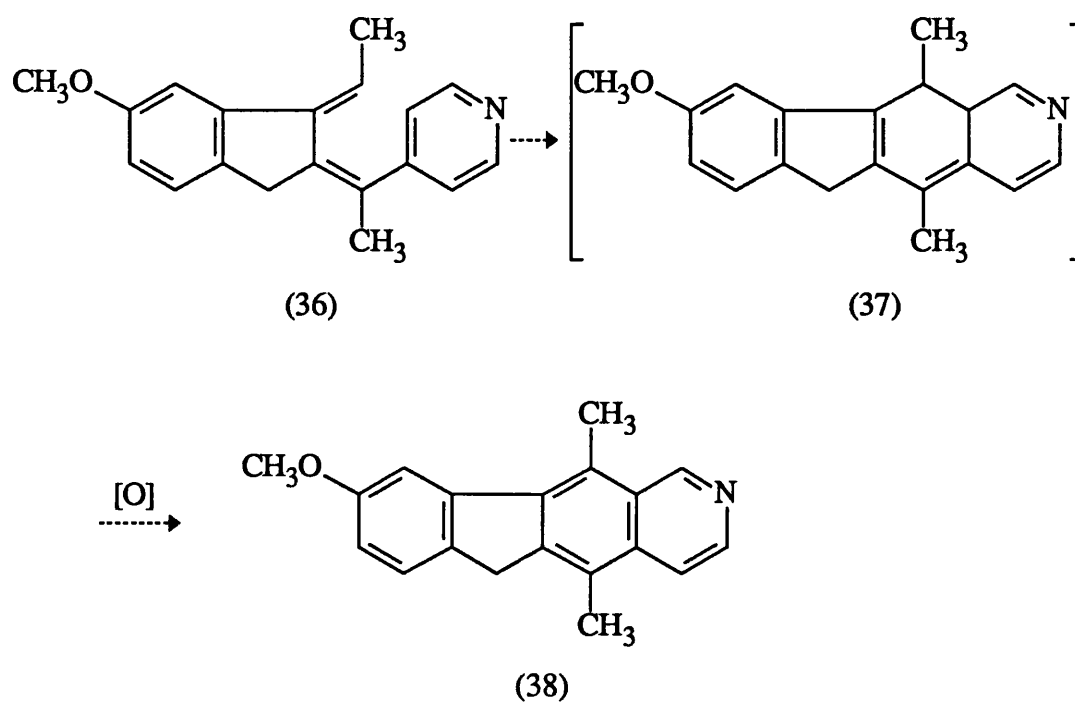
For example, an attempt to couple the benzophenone (34; X = O, R = H) with palladium(II)acetate proved unsuccessful, and treatment of the bromobenzophenone (34; X = O, R = Br) with sodamide or potassium hydride to produce the fluorenone (35) *via* an aryne intermediate also failed, as did base treatment of 2-bromo-4-methoxy-2',5'-dimethyldiphenylmethane (34; X = H₂, R = Br).



Attempts to prepare 2-amino-4-methoxy-2',5'-dimethylbenzophenone (34; X = O, R = NH₂) in good yield proved difficult, and this problem prevented efforts to construct the fluorenone (35) *via* a Pschorr cyclisation. However, irradiation

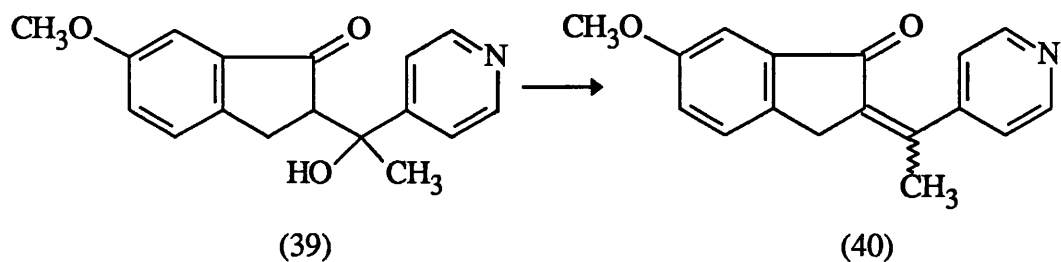
of the bromobenzophenone (34; X = O, R = Br) with ultraviolet light in methanol for four days produced the desired 6-methoxy-1,4-dimethylfluorenone (35), but in only 12 % yield. Since this step was just at the beginning of the synthesis of the tetracycle (32) it was considered that the low yield involved was insufficient to warrant further work.

In another approach Sainsbury and Popplestone envisaged that the desired tetracycle could be obtained by oxidative thermal cyclisation of the diene (36) (scheme 4).

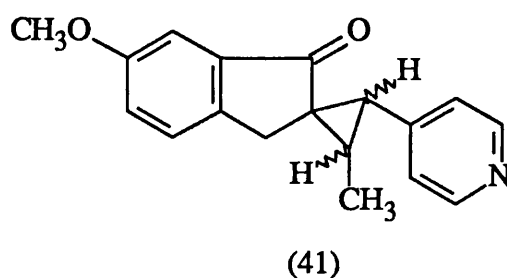


Scheme 4.

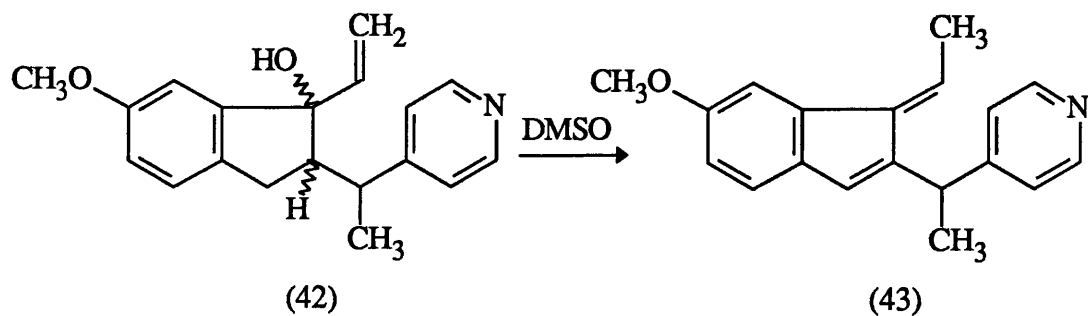
Reaction of the lithium enolate of 6-methoxyindanone with 4-acetylpyridine afforded the hydroxyketone (39) which, when treated with thionyl chloride in pyridine, dehydrated to give the enone (40) as a mixture of *E*- and *Z*-isomers in approximately equal amounts.



The *E*-isomer was separated and reacted with ethylene triphenylphosphorane, but this yielded the cyclopropane derivative (41), rather than the desired diene (36).



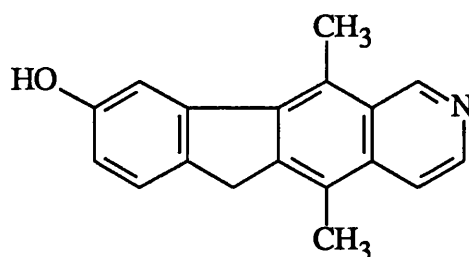
This result, although disappointing, was not entirely unexpected for similar products do occur as the result of reactions between phosphoranes and sterically hindered enones.⁴² It was also discovered that the enone failed to react either with ethyllithium or with ethylmagnesium bromide. The *Z*-isomer behaved similarly. Reduction of the enones and reaction with vinylmagnesium bromide yielded the alcohol (42) which could not be dehydrated satisfactorily under a number of conditions (heating with silica, basic alumina or potassium bisulphate, treatment with methanolic hydrogen chloride), but heating strongly with dimethyl sulphoxide afforded a single product which proved to be the diene (43).



the author then began to take up the challenge presented by the seemingly straightforward target presented by the tetracycle (32).

2. DISCUSSION

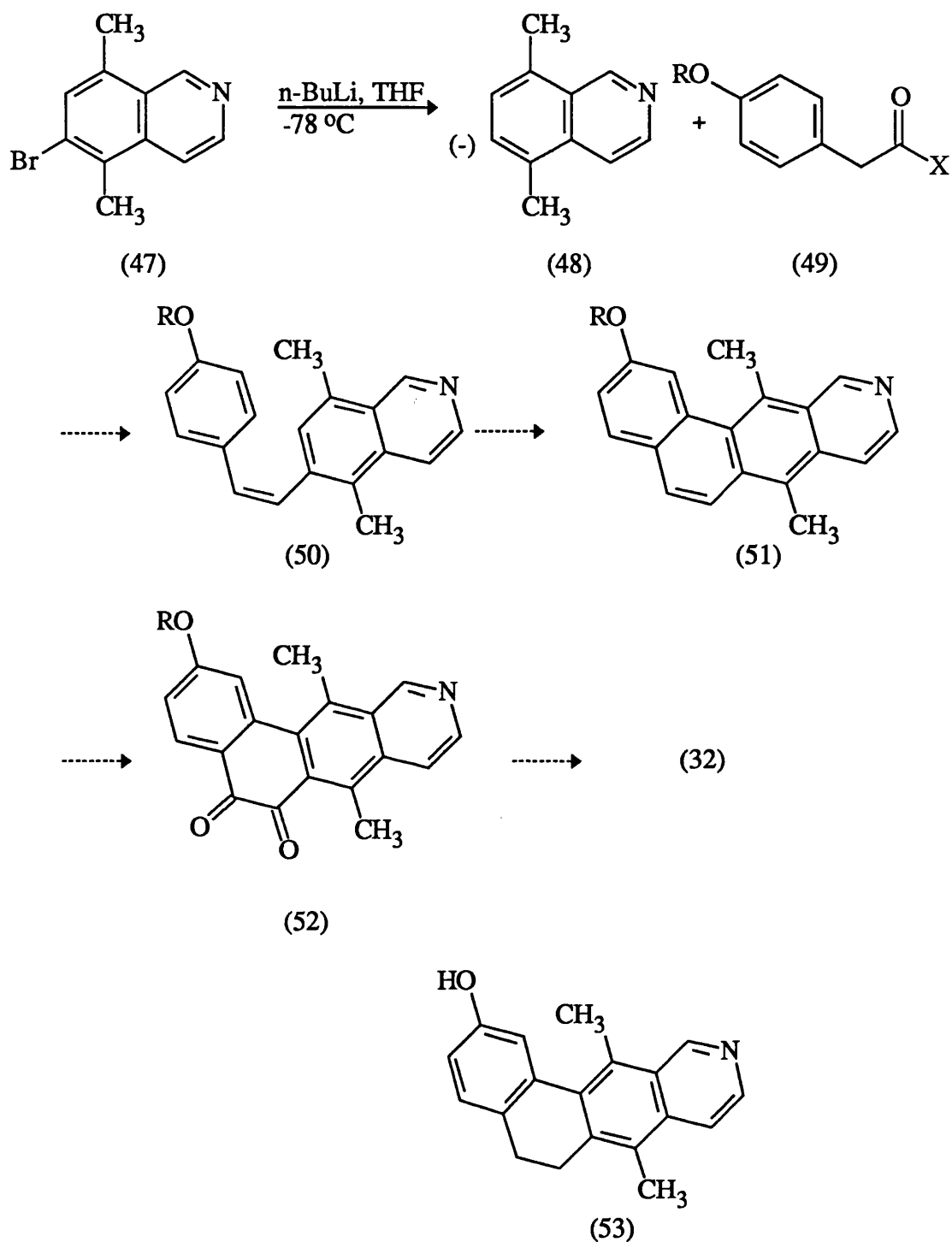
The literature relating to the target compound 9-hydroxy-5,11- dimethyl-6*H*-pyrido[4,3-*b*]fluorene * (32) and its derivatives is sparse and apart from previous work in this department by Popplestone the only other publication of note is that of Dixit, Khanna and Anand ³⁹, the contents of which have been described in the introduction.



(32)

At the commencement of the project we decided to make use of some of Popplestone's chemistry and to utilise the anion of the isoquinoline (47), used to prepare the acid chloride (44). Thus a condensation between the anion (48) and a suitable substrate (49) would, after subsequent reaction, give the pyridostilbene (50) which could be ring - closed to the pyridophenanthrene (51) by exposure to ultraviolet light and an oxidising agent. Further oxidation of this product to the orthoquinone (52), could lead, *via* ring contraction, to our desired target (scheme 5). At the same time we considered that the pyridophenanthrene (51, R = H) and its 10,11-dihydroderivative (53) would be interesting candidates for screening in their own right as potential anticancer agents.

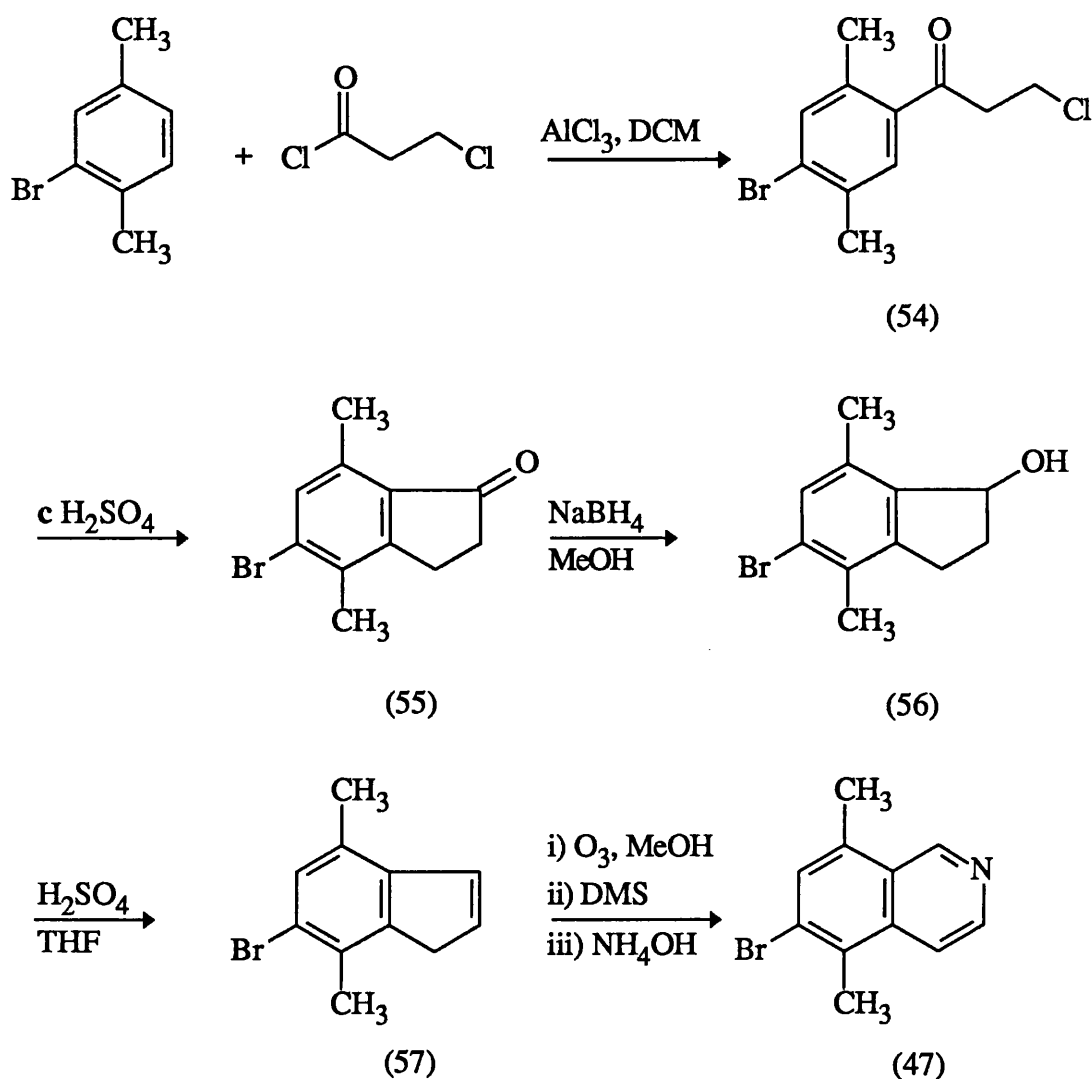
* The parent tetracycle is named and numbered in accordance with the system used for ellipticine (1), of which it is regarded as the 6-carbon analogue. Thus these compounds are regarded as pyrido[4,3-*b*]fluorenes, rather than as indeno[2,1-*g*]-isoquinolines. The latter nomenclature is in fact in line with IUPAC rules and is used in Chemical Abstracts.



Scheme 5.

Therefore our first synthetic target was 6-bromo-5,8-dimethylisoquinoline (47) which was prepared by the method of Miller and Moock⁴⁴ as shown in scheme 6. Thus a Friedel - Crafts reaction between 2-bromo-4-xylene and 3-chloropropionoyl chloride afforded the chlorobenzophenone (54) in 78 % yield. (Trituration of this

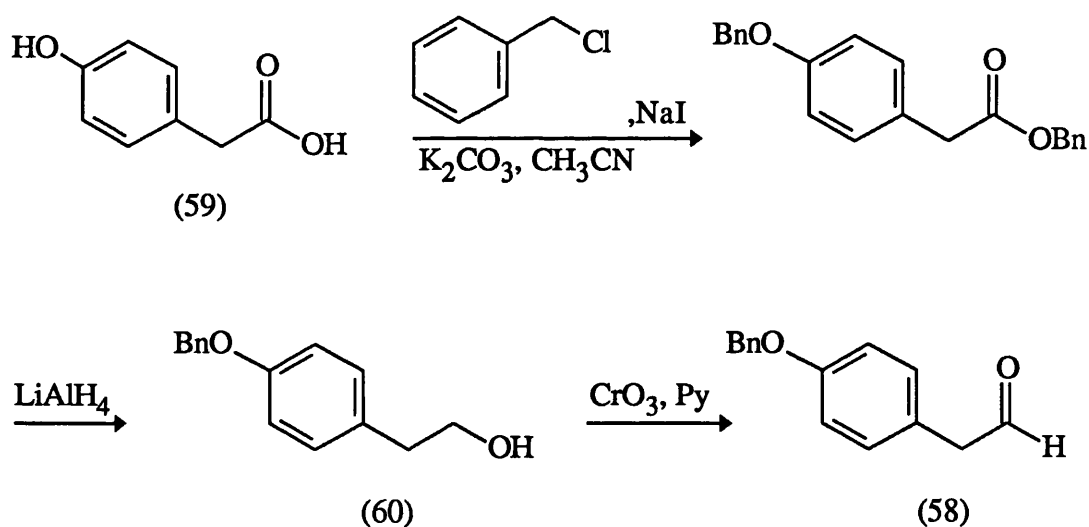
product with methanol gave a much cleaner product than in previous work and greatly facilitated the next step). Heating this compound with concentrated sulphuric acid at 90 °C for one hour resulted in the formation of 5-bromo-4,7-dimethylindanone (55) in 77 % yield. From this sodium borohydride reduction formed the indanol (56) (99 %), which was dehydrated to the indene (57) by heating with 5 M sulphuric acid in tetrahydrofuran in 95 % yield.



Scheme 6.

The final step utilised Miller and Frincke's ⁴⁵ indene to isoquinoline sequence. Thus ozonolysis of the indene (57) in the presence of methanol, followed by reductive work - up with dimethyl sulphide in the presence of sodium bicarbonate and then treatment with 2 M ammonium hydroxide yielded, after chromatography, the bromoisoquinoline (47) in 65 % yield (37 % overall from the bromoxylene).

Our first choice of carbonyl compound was 4-phenyloxyphenylacetaldehyde (49, R = Bn, X = H) which would give, upon reaction with the anion, an alcohol and thence the stilbene (50, R = Bn) after dehydration. The benzyl protecting group could readily be removed by hydrogenolysis. The protected aldehyde (58) had been previously prepared by Hedges and Herbert ⁴⁶ in three steps from 4-hydroxyphenylacetic acid (59) (scheme 7).

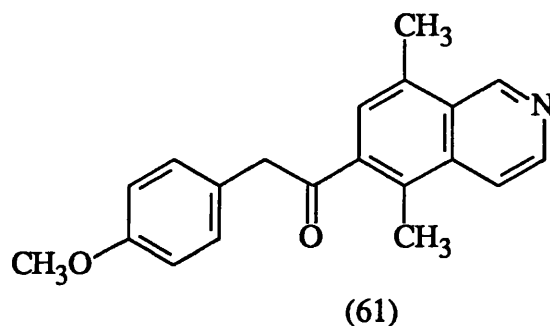


Scheme 7.

In our hands reaction of 4-hydroxyphenethyl alcohol with potassium hydroxide and benzyl chloride afforded the protected alcohol (60) in 61 % yield. Pyridinium chlorochromate ⁴⁷ oxidation of this product gave the desired aldehyde, but in only 32 % yield after purification (as the bisulphite salt). This was disappointing because Hedges and Herbert had achieved the oxidation step in 98 % yield (crude) by using Collin's reagent. Nevertheless we had sufficient material to work with, and reaction of

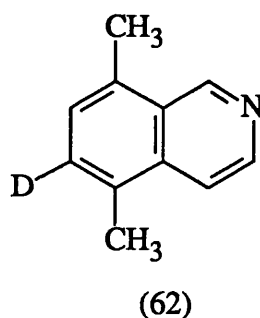
the isoquinoline anion (48) with the aldehyde (58) afforded a multicomponent mixture after work - up for bases. Unfortunately the ^1H n.m.r. spectrum of this mixture showed none of the expected signals for a product which might form from the two reactants. For example, the 5-proton singlet at δ 7.5 for the benzyl protons was absent, but the isoquinoline methyl proton signals were present at δ 2.5 and δ 2.65.

The reasons for this failure were not immediately clear, and we next considered that 4-methoxyphenylacetyl chloride (49, R = CH₃, X = Cl) might prove to be a more useful substrate and give the ketone (61) which could be reduced and dehydrated to the stilbene (50).

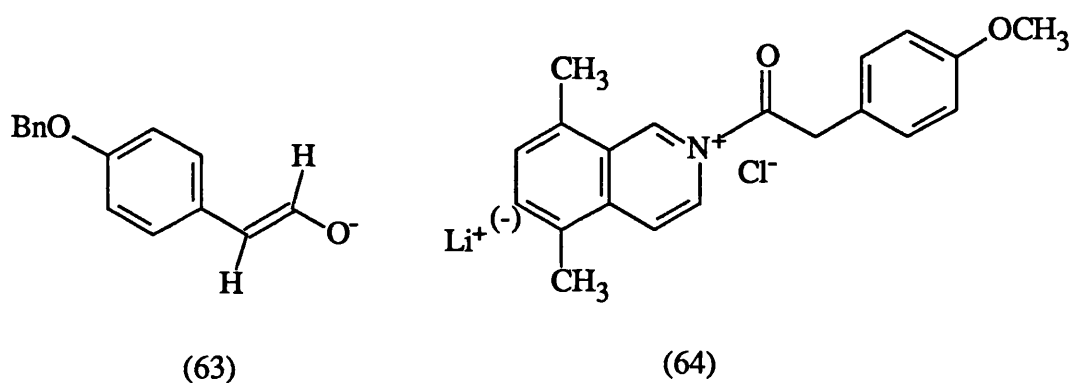


The acid chloride was prepared in 97 % yield by reaction of 4-methoxyphenylacetic acid with thionyl chloride, but reaction of it with the isoquinoline anion (48) produced the same result as the aldehyde reaction. Similarly reaction of ethyl 4-methoxyphenylacetate (49, R = CH₃, X = OC₂H₅) (from the corresponding acid and ethanol in 92 % yield) and the anion largely resulted in the recovery of the unreacted ester.

A model reaction between the anion and phenylacetaldehyde also afforded a complex mixture, showing no evidence of coupling. At this point we thought that it was necessary to confirm that the anion was being formed in reasonable yield and thus the putative anion was quenched with deuterium oxide. On work-up 6-deutero-5,8-dimethylisoquinoline (62) was isolated in 61 % yield.



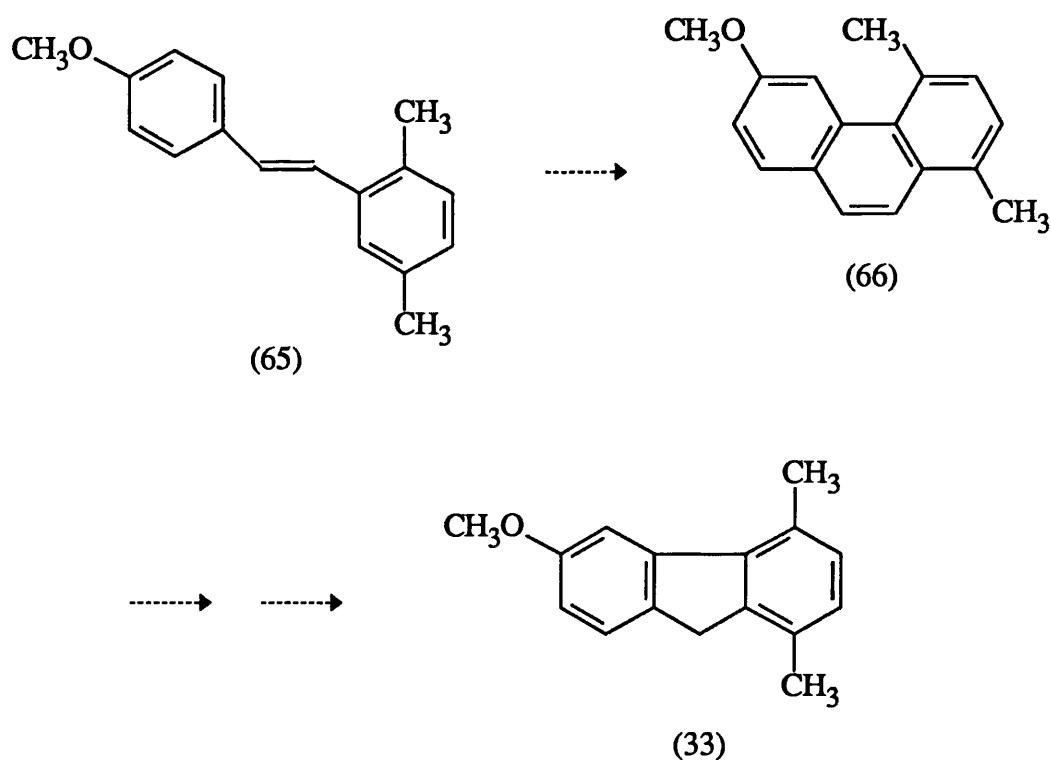
Although the yield was modest it does seem that enough of the anion should be present to afford reasonable amounts of coupled products and thus it would appear that the isoquinoline anion (48) is acting principally as a base rather than as a nucleophile, deprotonating the acidic methylene protons of the aldehyde (58) and generating the enolate (63) which could then undergo further condensation with unreacted aldehyde.



Similar chemical behaviour can be envisaged for phenylacetaldehyde used in the model reaction, although no evidence of any condensation products was determined. Deprotonation of the ester (49, R = CH₃, X = OC₂H₅) is also feasible and since this is a less active substrate it probably remained as the enolate derivative until work - up. Similarly there are several possible fates for the acid chloride (49, R = CH₃, X = Cl) including deprotonation, or reaction with the lone pair electrons of the isoquinoline ring nitrogen to afford an acylium complex (64). In any event no discernable reaction product could be isolated and much time was invested in attempting unsuccessfully to separate multicomponent mixtures.

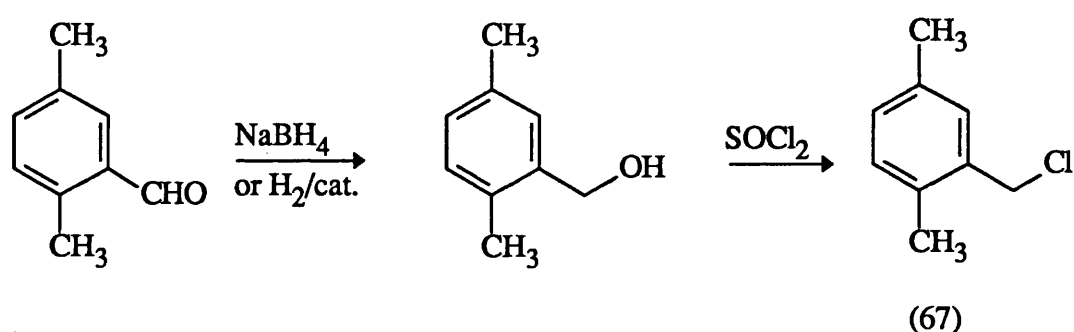
The ^1H n.m.r. spectrum of the mixture does however, resemble that of the 6-deuteroisoquinoline (62). For instance two singlets of equal intensity at δ 2.55 and δ 2.68 are observed which correlate with similar signals in the spectrum of this compound. Thus it seems that a major product is 5,8-dimethyloisoquinoline, as would follow if its anion acted simply as a base.

At this point we decided not to explore this approach further, but rather to look at the feasibility of the photochemical cyclisation of the stilbene (65) to the phenanthrene (66) and its subsequent conversion to the fluorene (33) (scheme 8). Indeed this is a key reaction in our approach for the fluorene is an important intermediate in the various routes proposed earlier.



Scheme 8.

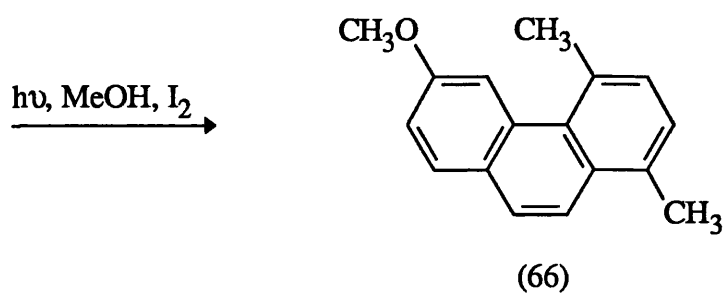
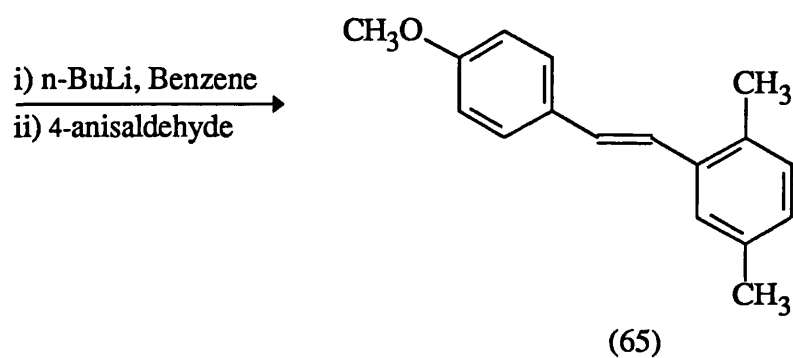
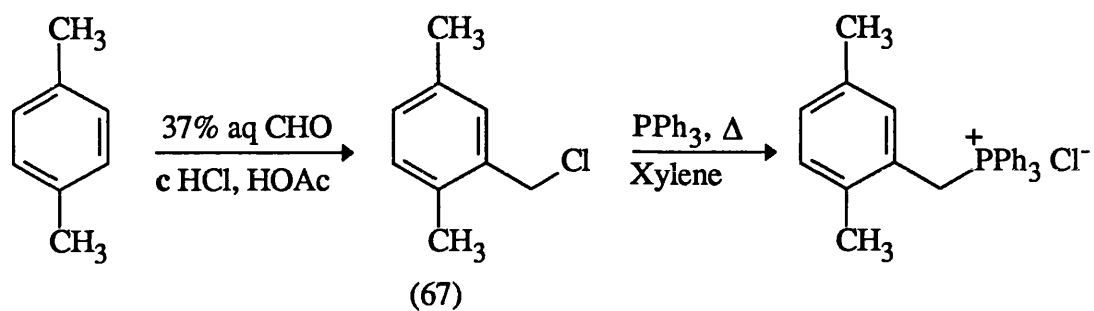
A search of the literature revealed that both the stilbene and the phenanthrene are known,⁴⁸ and the latter is produced by photochemical cyclisation of the stilbene. Unfortunately the author of this work was more interested in the ¹H n.m.r. spectrum of the phenanthrene than its preparation and the experimental details are sparse, in fact Letcher simply stated that the stilbene required was prepared using “Wittig methodology”. Clearly there are two ways of tackling this synthesis, either a reaction between 4-methoxybenzyltriphenylphosphonium halide and 2,5-dimethylbenzaldehyde, or that between 2,5-dimethylbenzyltriphenylphosphonium halide and 4-anisaldehyde. Letcher cited an earlier paper⁴⁹ in which the necessary benzyl chloride was obtained from the corresponding benzyl alcohol using thionyl chloride. The benzyl alcohol, in turn, was prepared by reduction of the corresponding aldehyde (scheme 9).



Scheme 9.

This sequence seems somewhat irrelevant since chloroformylation of 4-xylene should give the benzyl chloride (67) directly. In fact this product has already been prepared in this way⁵⁰ and in our hands this gave the benzyl chloride in 69 % yield. Conversion into the phosphonium chloride is also reported,⁵¹ and following this procedure the salt was produced in 87 % yield and reacted with n-butyllithium to afford the ylide. 4-Anisaldehyde was then added to the reaction mixture and the stilbene (65) was obtained in 70 % yield (scheme 10). As stated earlier, the experimental detail in Letcher's paper is sparse, and no spectroscopic data is quoted for the stilbene.

However, his product and ours have similar melting points and the ^1H n.m.r. spectrum of our compound showed all the expected resonances for the *E*-isomer (65) (see experimental section).



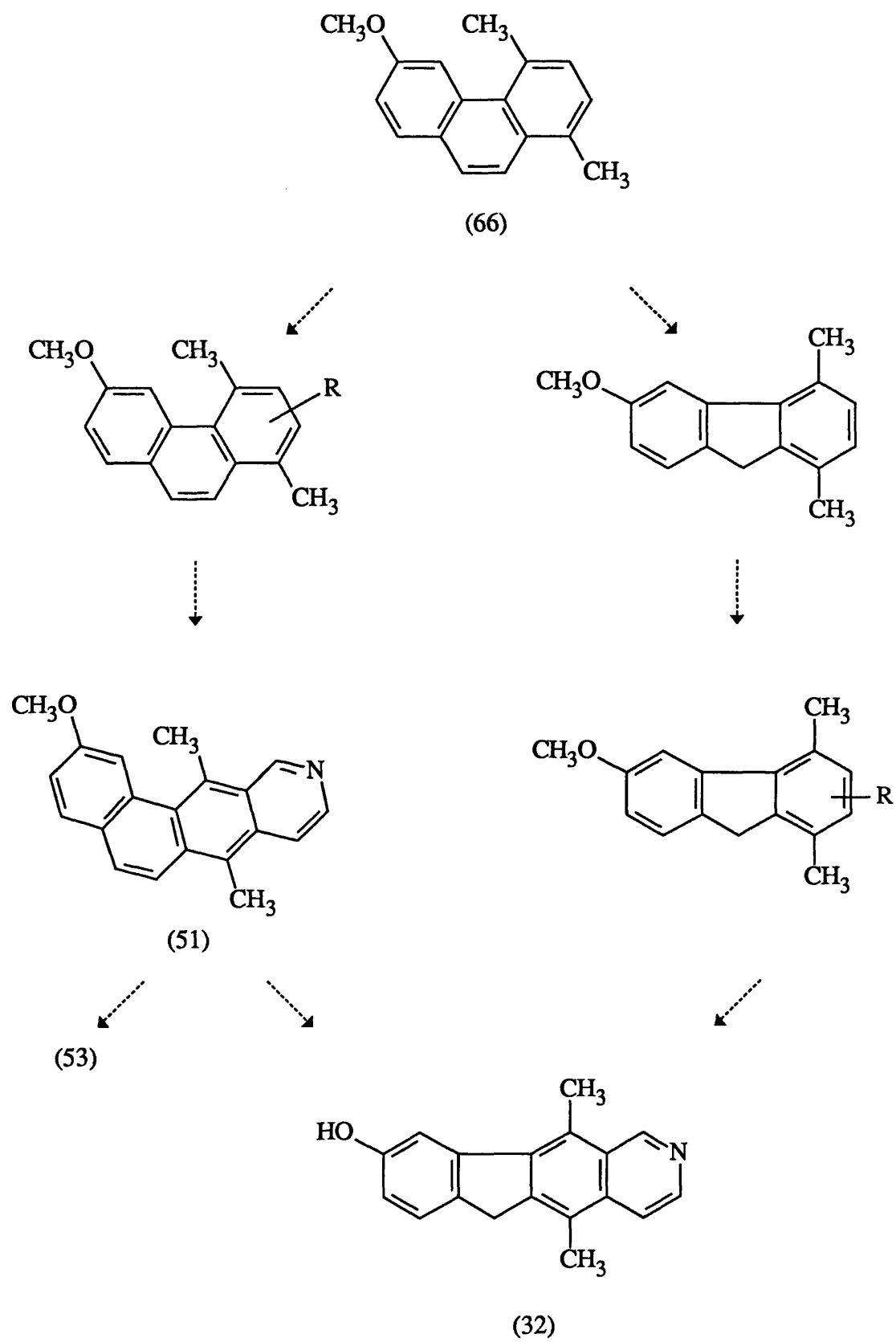
Scheme 10.

Following Letcher's conditions⁴⁹ the stilbene (65) was irradiated using a 400 W medium pressure mercury lamp, in cyclohexane with iodine as an oxidant. The reaction was followed by ultraviolet spectroscopy, monitoring the disappearance of the maximum absorbance of the stilbene at 295 nm and the appearance of a new maximum at 255 nm after 1.5 hours. A colourless solid was isolated in poor yield (20 %) from the crude product, which had a melting point of 70 °C, different from the one quoted by Letcher at 82 - 83 °C.⁴⁸ The ¹H n.m.r. spectrum is, however, fully compatible with the required compound and spin - spin patterns due to the ABX system of the methoxylated ring protons (including the bay - region proton at δ 8.22) and the AB system for the signals of protons 2 and 3 is clearly visible. The protons at 9 and 10 resonate together as a singlet at δ 7.29 (see experimental section).

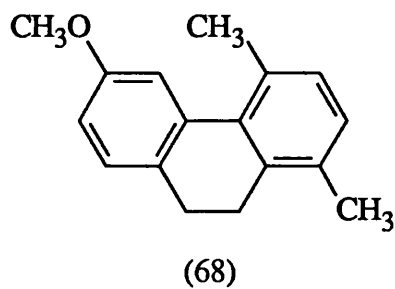
Improved yields of between 50 and 70 % were achieved by performing the irradiation in methanol solution using iodine as an oxidant and agitating the mixture by the passage of dry air for one hour.

Having obtained 6-methoxy-1,4-dimethylphenanthrene (66) two options were open to us. Thus we might build up ring-D of the pyridophenanthrene and then contract the B-ring or reverse the order of these processes (scheme 11).

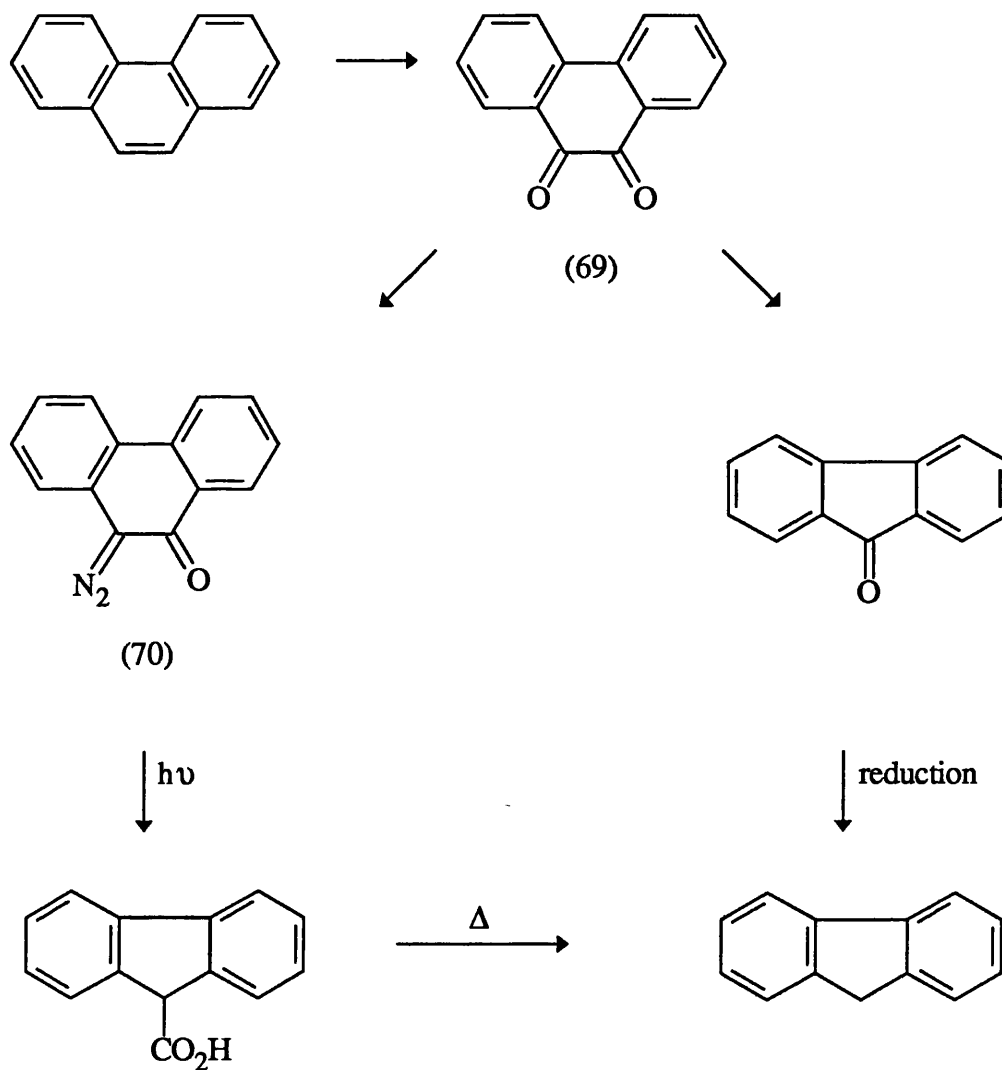
We decided to investigate both approaches in parallel. However, Vilsmeier formylation of the phenanthrene failed and starting material was returned even after heating at 100 °C. This was surprising since at least we anticipated formylation at C-9. Indeed to counteract this possibility we used a slight modification of Harvey *et al.*'s⁵² procedure for the reduction of phenanthrenes to 9,10-dihydrophenanthrenes and obtained the derivative (68) in 86 % yield. However, further work on this compound was shelved because of the results to be described later.



Scheme 11.

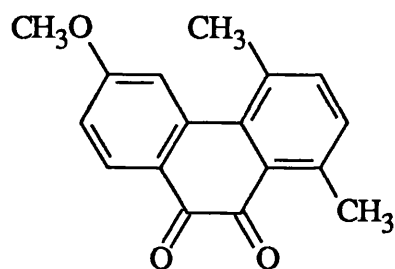


In the case of phenanthrene itself ring - contraction to fluorene has been achieved in two ways, both of which require initial oxidation to the 9,10-quinone (69). In one case ⁵³ a benzil - benzilic acid rearrangement is then employed and in the other a Wolff rearrangement of the derived α -diazoketone (70) is required ⁵⁴ (scheme 12).

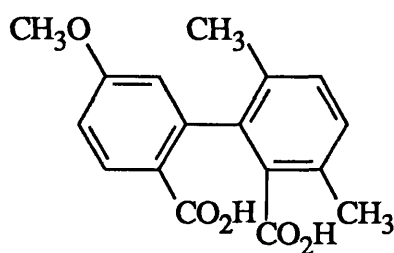


Scheme 12.

The method of choice ⁵⁵ for the oxidation of phenanthrene to 9,10-phenanthrenequinone (69) is treatment with chromium(VI) oxide in sulphuric acid, but for our substrate oxidation under these circumstances afforded a very complex mixture from which none of the desired 6-methoxy-1,4-dimethyl-9,10-phenanthrenequinone (71) could be isolated. The most likely causes of this disappointing outcome are over oxidation to the diphenic acid (72) and competing oxidation of either or both of the methyl groups.



(71)

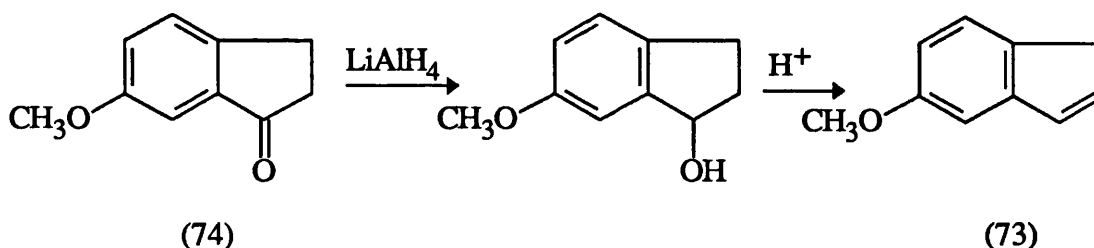


(72)

As with the studies towards D-ring formation no further work was conducted in this area simply because of logistic problems. Thus the best laboratory scale yields of phenanthrene (66) were obtained when 500 mg of the stilbene (65) was reacted in 1.2 litres of methanol for one hour. Clearly this is a very inefficient process and in an attempt to improve productivity some large scale cyclisations were carried out in a 15 litre reaction vessel. Three grams of stilbene were reacted in 9.2 litres of methanol for 2.25 hours. At the end of this time only 58 % of the mass was recovered and the product proved to be a 1:1 mixture of the desired phenanthrene (66) and unreacted stilbene (65). Because of this poor result and in the light of the oxidation reaction we decided to leave approaches based on the photochemical cyclisation and turned to a more direct route to the intermediate fluorene (33).

The Diels - Alder reaction as a method for the synthesis of fluorenes has been used in two ways: 1) thus a reaction between cinnamic acid and 1,3-butadiene gives biphenyl-2-carboxylic acid which cyclises under the reaction conditions to fluorenone forming the B-ring in the final step. ⁵⁶ 2) A reaction of indene with 1,3-butadiene is known to produce tetrahydrofluorene. ⁵⁷

The first approach was used by Dixit, Khanna and Anand ³⁹ in their synthesis of the parent tetracycle. However, in Popplestone's work ⁴⁰ an analogous reaction between 3-methoxycinnamic acid and 2,4-hexadiene failed. We considered that the second approach looked attractive. Thus a reaction between 5-methoxyindene (73) and a suitable diene would lead quickly to the desired fluorene (33). On reflection we decided against using 5-methoxyindene for two reasons. Firstly the synthesis of 5-methoxyindene (73) ⁵⁸ requires the preparation of 6-methoxy-1-indanone (74) ⁵⁹ which is difficult, although the remaining two steps are straightforward (scheme 13).



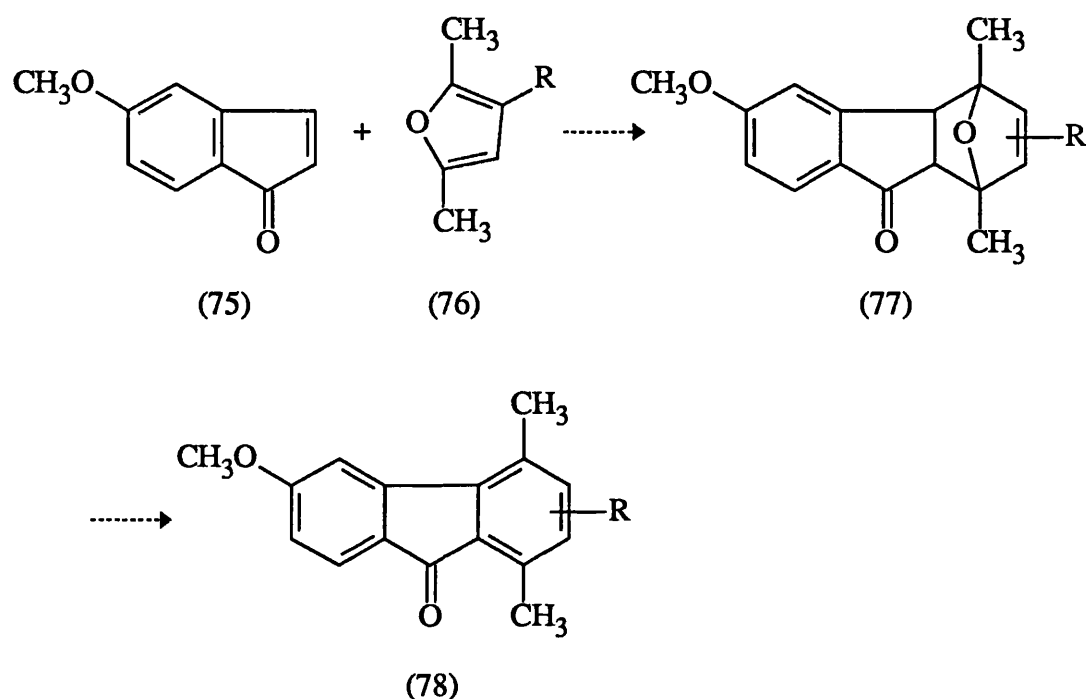
Scheme 13.

Secondly there is evidence for the isomerisation of 5-methoxyindene to 6-methoxyindene ⁶⁰ and House has found that substituted indenenes under the conditions of the Diels - Alder reaction give mixed products. ⁶¹

Indenones, however, have been used as dienophiles in the synthesis of fluorenones. ⁶² This offers the advantage that the double bond position is fixed and the substrate is a much more reactive dienophile. Furans have been used successfully as dienes in Diels - Alder reactions ⁶³ and Brion ⁶⁴ has found that the addition of zinc iodide is an effective catalyst for cycloadditions of this type. Indeed workers at Bath

have often successfully used this Lewis acid in related reactions.⁶⁵

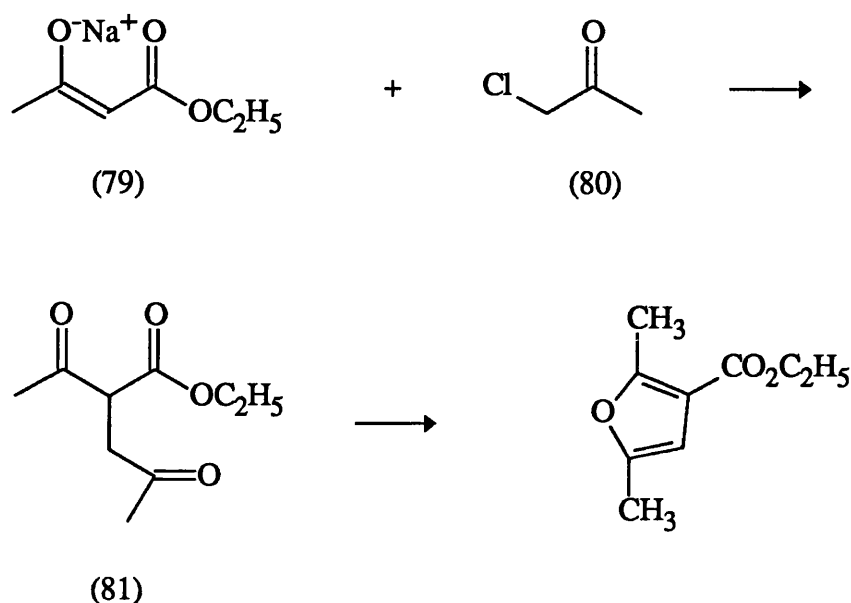
We envisaged that a Diels - Alder reaction between 5-methoxy-1-indenone (75) and 2,5-dimethylfuran (76, R = H) would give the adduct (77, R = H) which could be aromatised to the fluorenone (78, R = H) (scheme 14).



Scheme 14.

Extending this we considered that a 3-substituted-2,5-dimethylfuran (76, R \neq H) would provide a handle for the elaboration of the pyridine ring to complete the synthesis. A search of the literature revealed that ethyl 2,5-dimethylfuran-3-carboxylate (76, R = CO₂C₂H₅) was known^{66,67} and so we set out to synthesise these two molecules.

Treatment of the sodium salt of ethyl acetoacetate (79) with monochloroacetone (80) resulted in the formation of ethyl α -acetylacrylate (81)⁶⁶ in 67 % yield, which on standing cyclised to ethyl 2,5-dimethylfuran-3-carboxylate (76, R = CO₂C₂H₅) in 54 % overall yield (scheme 15).

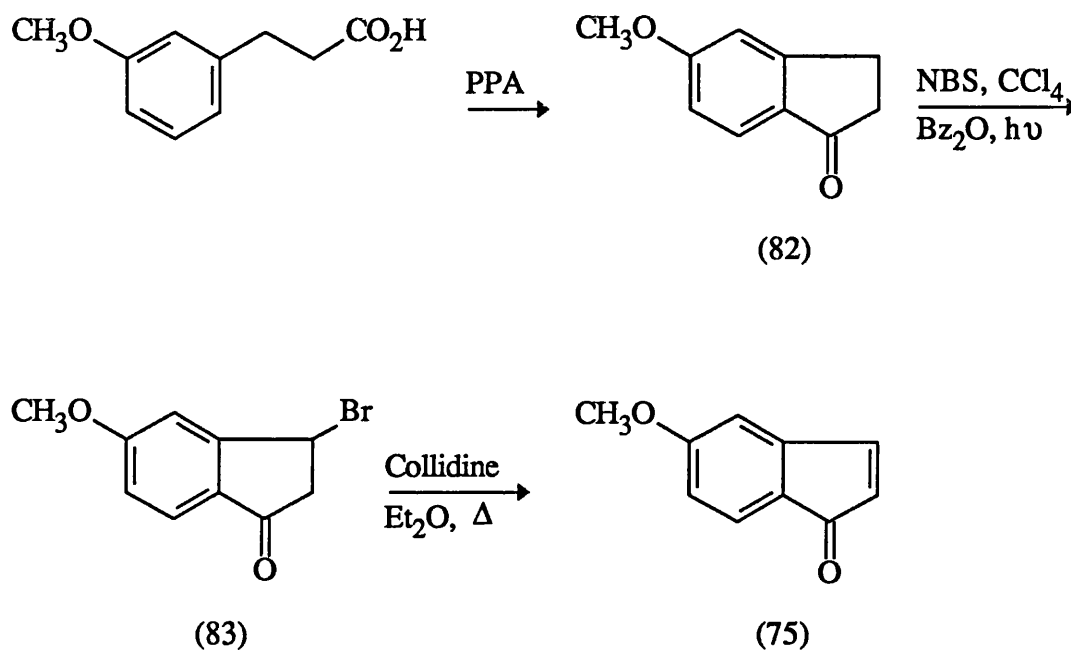


Scheme 15.

5-Methoxy-1-indenone (75) is mentioned in a Japanese patent ⁶⁸ as a product in the reaction of substituted benzenes, acetylenes and carbon monoxide in the presence of rhodium complexes. In addition Friedrich and Tam ⁶⁹ have prepared 5-methoxy-1-indenone as an intermediate in their 4-step synthesis of 5-methoxyindan-1-yl-3,5-dinitrobenzoate. Clearly the first method is impractical and Friedrich and Tam's synthesis was undertaken thus.

Reaction of 3-methoxyphenylpropionic acid with polyphosphoric acid at 50 °C for three hours afforded 5-methoxy-1-indanone (82) in 84 % yield. ⁷⁰ Treatment of this product with *N*-bromosuccinimide afforded the desired 3-bromo-5-methoxy-1-indanone (83) in 70 % yield. This yellow solid shows a distinct ¹H n.m.r. spectrum thus the methylene protons at C-2 resonate as a geminal pair (signals at δ 3.0 and δ 3.5, $J_{\text{gem}} = 16$ Hz), each independently coupled with the resonance of H-3 (δ 5.5). The last signal is observed as a double doublet, $J_1 = 8$ Hz, $J_2 = 4$ Hz and thus the entire spin - spin system approximates to that of an ABX pattern.

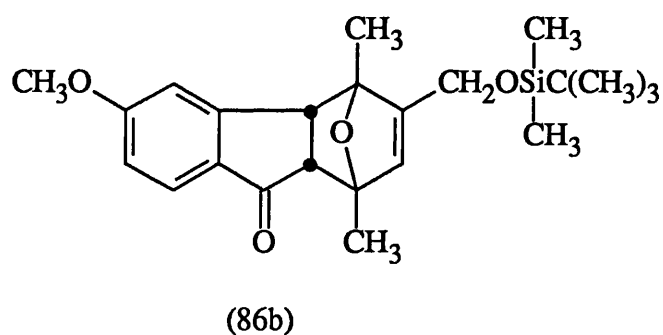
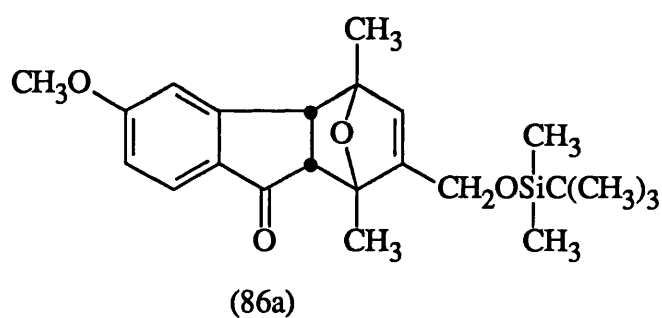
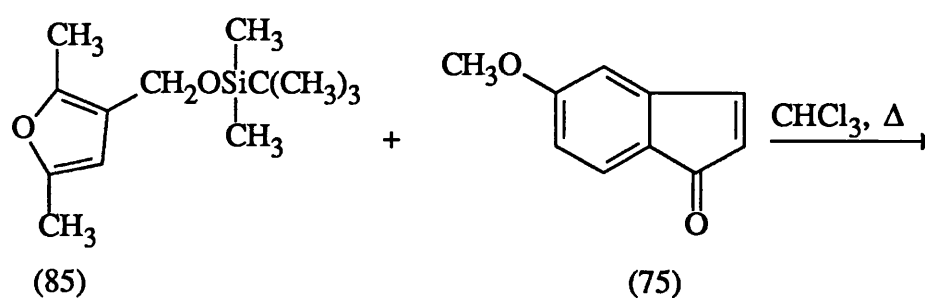
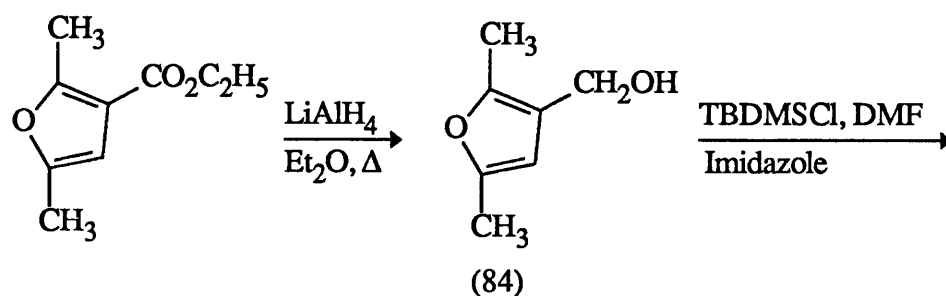
Dehydrobromination of the bromoindanone with 2,4,6-collidine in ether produced the desired 5-methoxy-1-indenone (75) in 84 % yield (scheme 16) (overall 59 % from the indanone) comparing favourably with Friedrich and Tam's approximate 45 % yield after two steps.



Scheme 16.

We speculated that the ester group at C-3 in the furan (76) might influence the regioselectivity of the cycloaddition reaction between it and the indenone. However, since this reactant is somewhat electron deficient we were not surprised when the Diels-Alder reaction failed and the furan was returned unchanged. Reduction to the corresponding alcohol should prevent this problem and this was achieved by reaction with lithium aluminium hydride using Baxter's conditions.⁷¹ However, a reaction between 5-methoxy-1-indenone (75) and 2,5-dimethylfuran-3-methanol (84) under reflux in toluene produced a complex mixture showing no firm evidence of an adduct. This is not surprising since the alcohol (84) is unstable and darkens rapidly on standing and secondly the indenone (75) is only sparingly soluble in toluene. These two facts

probably account for this result.



Scheme 17.

Fortunately the t-butyldimethylsilyl ether of the alcohol is quite stable and a cycloaddition reaction between the protected furan (85) and 5-methoxy-1-indenone (75)

in boiling chloroform for 48 hours produced a mixture from which a colourless solid was isolated in 33 % yield (scheme 17). (An improvement in the rate, but not the yield was found when zinc iodide was added as catalyst.) Spectroscopic analysis of this product showed that it contained a mixture of the two adducts (86a) and (86b) in an approximate ratio of 2:1. * Since the substituent group of the furan is no longer conjugated with the ring, this lack of selectivity is understandable and, for example, the ^1H n.m.r. spectrum of the product shows four distinct methyl groups, the protons of which resonate as two pairs of singlets at δ 1.75, 1.77 and δ 1.62, 1.66.

Preparative thin layer chromatography enabled a sample of the major isomer to be obtained and its general structure confirmed as the adduct (86) (see experimental).

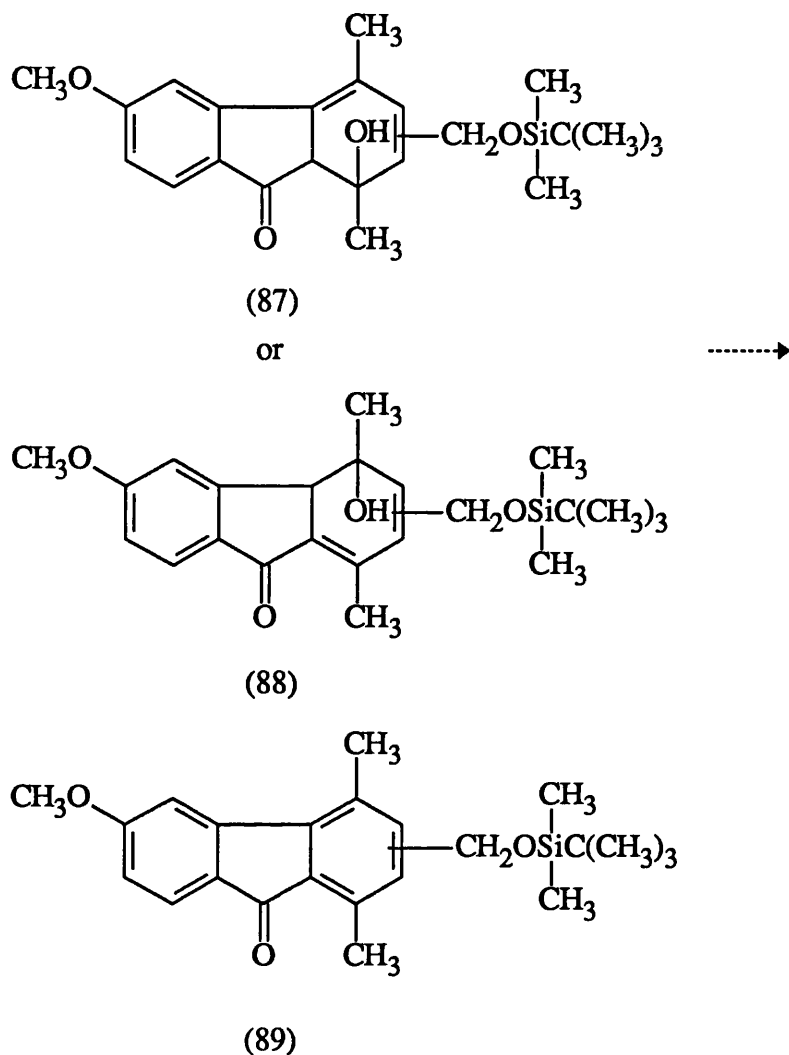
Rather than attempting a difficult separation at this stage we wondered if the fully aromatised adducts might be easier to deal with. Brion found that lithium hexamethyldisilazide effects ring opening of adducts of this type *via* β -elimination of the oxygen bridge to form a cyclohexadiene.⁶⁴ In our case two types of products might form i.e. the alcohols (87) and (88). We considered that dehydration of these alcohols should occur readily to give the fluorenones (89) (scheme 18).

Treatment of the adducts (86a and b) with lithium hexamethyldisilazide (generated from hexamethyldisilazane and n-butyllithium at -78 °C) failed to achieve this resulting largely in recovery of the starting material. In his paper Brion states that the use of other bases (potassium hydride or alkoxides at 50 °C) produced only a retro Diels - Alder reaction.⁶⁴

Aromatisation of furan Diels - Alder adducts has been achieved by reduction of the double bond, followed by treatment with concentrated sulphuric acid.⁷² Reduction of the mixed adducts proceeded smoothly at atmospheric pressure using 10 % palladium on charcoal as catalyst, but reaction of the crude product with concentrated sulphuric acid at 0 °C or under reflux with 1 M sulphuric acid produced multicomponent mixtures in both cases.

* In addition to the main spots on the t.l.c. plate 'shadow' spots were also visible indicating the probability of *exo* and *endo* isomers.

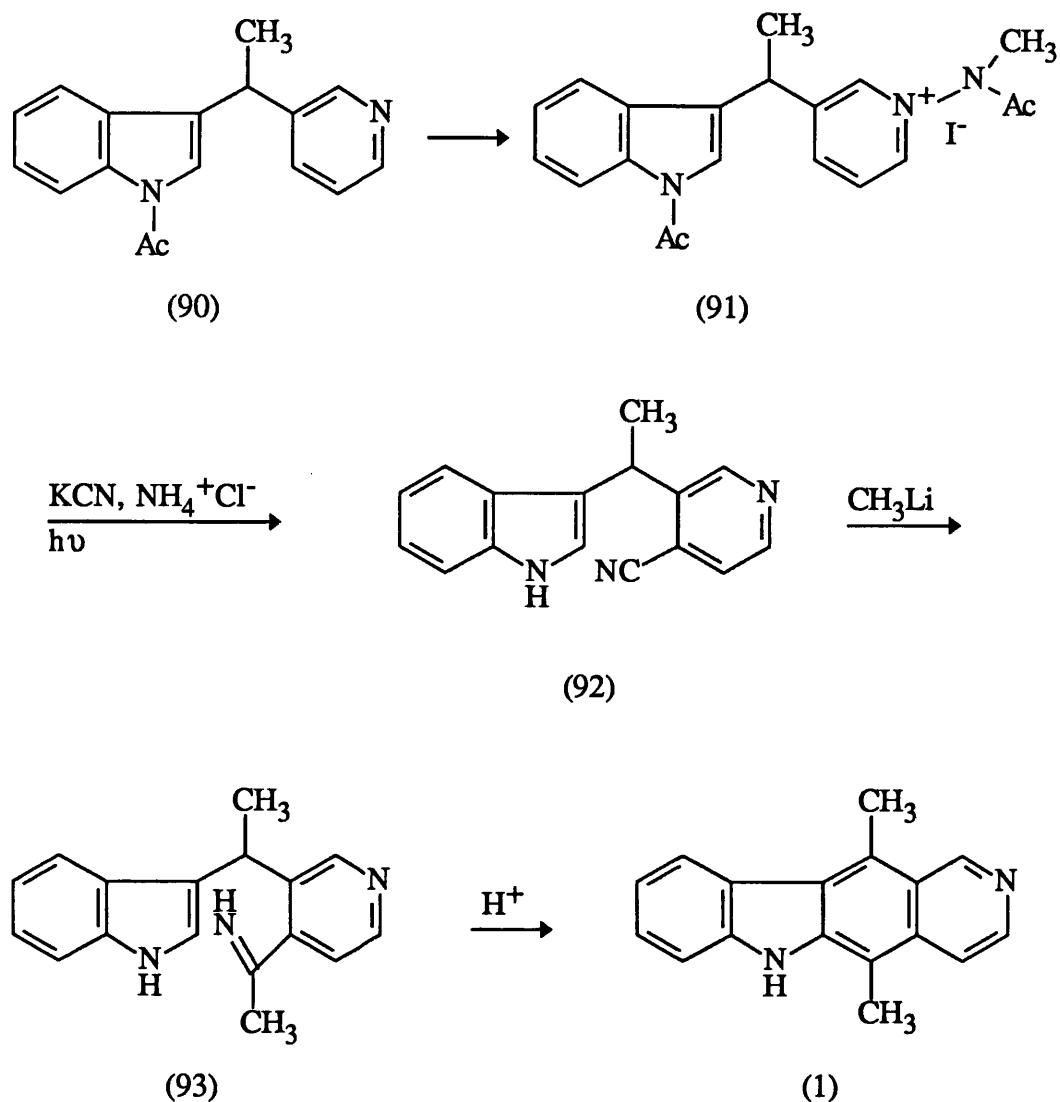
Heating the adducts with *N*-bromosuccinimide under spot lamp irradiation at 80 °C in carbon tetrachloride also produced a multicomponent mixture.



Scheme 18.

At this stage, because of the moderate yield in the Diels - Alder reaction and the non - selectivity which we had encountered we began to look elsewhere for a solution to our synthetic problem. Thus we directed our attention towards a more straightforward approach and one which would be convergent and would involve formation of the C-ring in the final steps. Our proposal was based upon some known chemistry developed at Bath towards the synthesis of ellipticine (1).⁷³ This is outlined

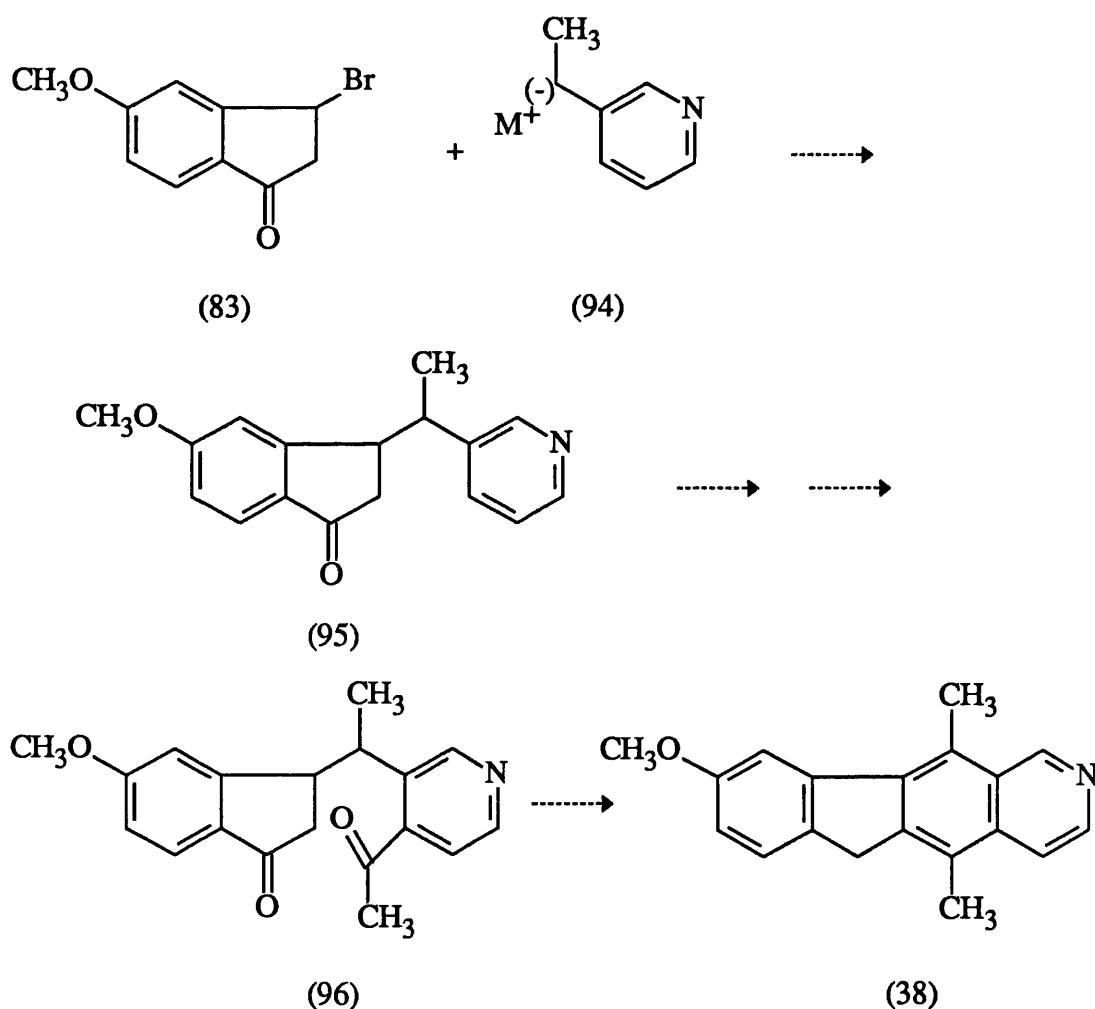
in scheme 19.



Scheme 19.

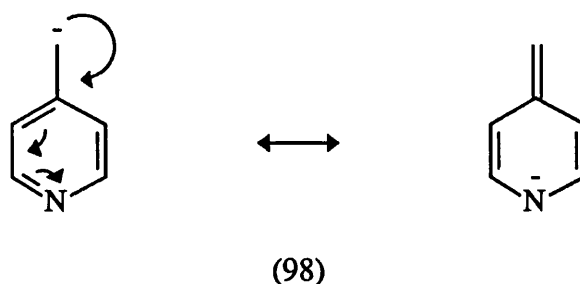
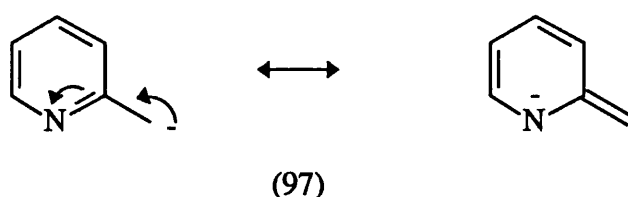
In this *N*-acetyl-3-[1-(3'-pyridyl)ethyl]indole (90) is treated with *O*-mesitylsulphonylhydroxylamine followed by reaction with acetic anhydride and methyl iodide to give the quaternary salt (91). Treatment of this with ammonium chloride and potassium cyanide followed by ultraviolet light gives the nitrile (92). Reaction of the nitrile with methyllithium gives the imine (93), hydrolysis of which, with acetic acid, affords ellipticine in good yield. This synthesis has proved quite versatile allowing a number of ellipticines to be prepared, with various substituents in the A-ring. It also allows for variations to be made at C-5 by choice of nucleophile.

Our proposed route is as outlined in scheme 20, thus reaction of 3-bromo-5-methoxy-1-indanone (83) (or a suitably protected form) with the anion of 3-ethylpyridine (94) would give us 5-methoxy-3-[1-(3'-pyridyl)ethyl]-1-indanone (95). Elaboration to the diketone (96) using the chemistry discussed previously should be straightforward and synthesis of our target *via* an intramolecular aldol reaction and subsequent aromatisation would follow. Indeed Tewari, Rastogi and Anand ⁷⁴ have shown that 5-methoxy-1-indanone will undergo the aldol condensation with carbonyl compounds. For example, condensation with 4-hydroxybenzaldehyde affords 2-(4'-hydroxybenzylidene)-5-methoxy-1-indanone in 80 % yield.



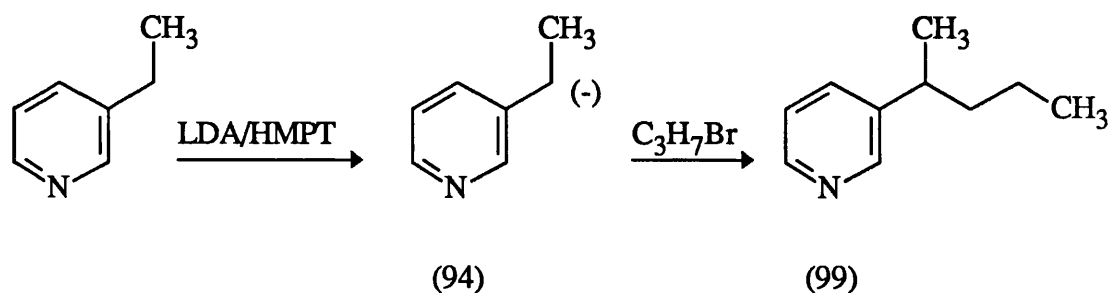
Scheme 20.

Our first consideration was the generation of the anion of 3-ethylpyridine. The methyl protons of 3-picoline (and by analogy, the methylene protons of any higher homologue) are not as acidic as those of 2- and 4-picoline. This is because in the case of 2- and 4-picolines the corresponding anions can be stabilised by delocalisation involving the ring nitrogen [*cf.* the canonical forms (97) and (98)]. No such stabilisation occurs for 3-picoline and generation of the anion is much harder although not impossible.⁷⁵



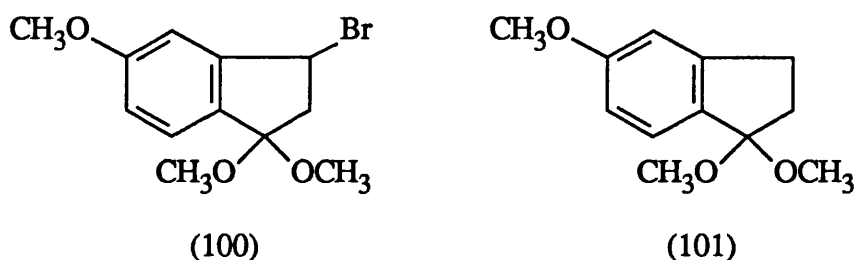
Thus Kaiser and Petty showed that 3-picoline when treated with lithium diisopropylamide (LDA) / hexamethylphosphoric triamide (HMPT) complex, followed by reaction with 1-bromopropane gives 3-butylpyridine in 77 % yield.

Despite this a search of the literature failed to find any examples of the generation of the anion of 3-ethylpyridine, but treatment of 3-ethylpyridine with LDA / HMPT following Kaiser and Petty's conditions⁷⁵ then quenching with 1-bromopropane afforded 3-(2'-pentyl)pyridine (99) in 45 % yield with 44 % recovery of 3-ethylpyridine (scheme 21).



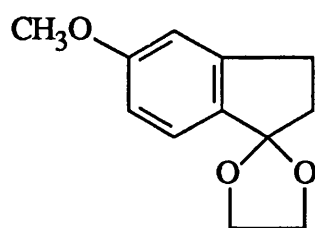
Scheme 21.

Encouraged by this result we formed the anion (94) and treated it with 3-bromo-5-methoxy-1-indanone (83) obtaining, after work-up, a complex mixture. This result was not very surprising as the substrate might react with a nucleophile at C-1, C-2 or at C-3 causing elimination as well as alkylation. In order to avoid this complication an attempt was made to form the acetal (100).

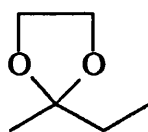


The use of orthoesters in acetal preparation from ketones has found success where direct reaction between ketone and alcohols is poor.⁷⁶ Reaction of the bromoindanone (83) with trimethylorthoformate and *para*-toluenesulphonic acid (*p*TSA) in methanol resulted in a black mixture which was composed predominantly of the starting bromoindanone. Treatment of the acetal (101) with *N*-bromosuccinimide should produce the bromoacetal (100) and so we decided to prepare 1,1,5-trimethoxyindan (101) instead. Stirring 5-methoxy-1-indanone with trimethylorthoformate and *p*TSA in methanol at room temperature returned only starting material after 24 hours. The same result was obtained when activated 4 Å molecular sieves were added to the reaction mixture, when the reaction mixture was heated under reflux in methanol or in boiling benzene using a Dean - Stark apparatus.

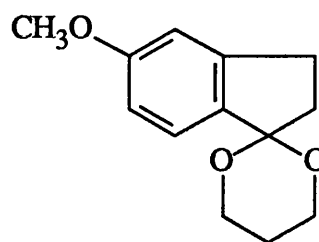
We considered that 2-(5'-methoxy-1'-indanyl)-1,3-dioxolane (102) might be easier to form, as cyclic acetals are often easier to form than open chain ones.⁷⁷ But, as in the orthoester approach, heating 5-methoxy-1-indanone under reflux in benzene with 1,2-ethanediol and *p*TSA in a Dean - Stark apparatus returned only starting material after 48 hours.



(102)



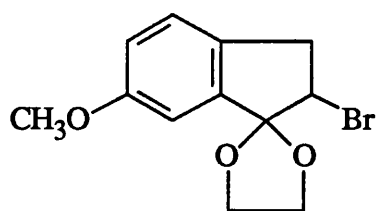
(103)



(104)

Dioxolane exchange has been reported to give better yields, in many cases, than direct reaction with 1,2-diols.⁷⁸ Treatment of 5-methoxy-1-indanone with neat 2-ethyl-2-methyl-1,3-dioxolane (103) and *p*TSA following Dauben's conditions yielded only recovered starting 5-methoxy-1-indanone. We considered that preparation of 2-(5'-methoxy-1'-indanyl)-1,3-dioxane (104) might be easier as the product would experience less strain. However, reaction of 5-methoxy-1-indanone with 1,3-propanediol and *p*TSA under reflux in benzene in a Dean - Stark apparatus for 24 hours returned, again, only starting material.

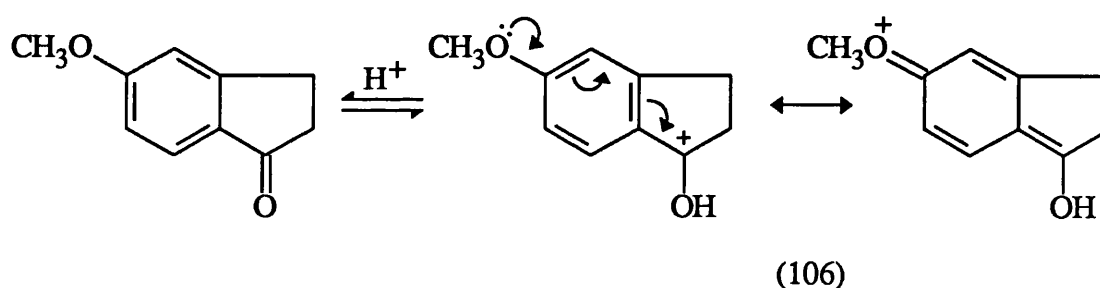
A search of the literature revealed that House and McDaniel⁷⁹ had prepared 2-(2'-bromo-6'-methoxy-1'-indanyl)-1,3-dioxolane (105) from 2-bromo-6-methoxy-1-indanone in 34 % yield using similar conditions to those we employed for the other isomer.



(105)

However, in this case the reaction time was three days and during this time an extra mol. equivalent of the diol was introduced. With our substrate even these conditions were insufficient returning the starting material unchanged. Eventually when the reaction time was increased to 5 days, using 5-methoxy-1-indanone, the desired acetal (102) was obtained albeit in only 10 % yield. The resonance of the C-4 and C-5 carbons in the dioxolane ring appears as a triplet at δ 64.96 in the ^{13}C n.m.r. spectrum, in good agreement with House's observations.⁷⁹

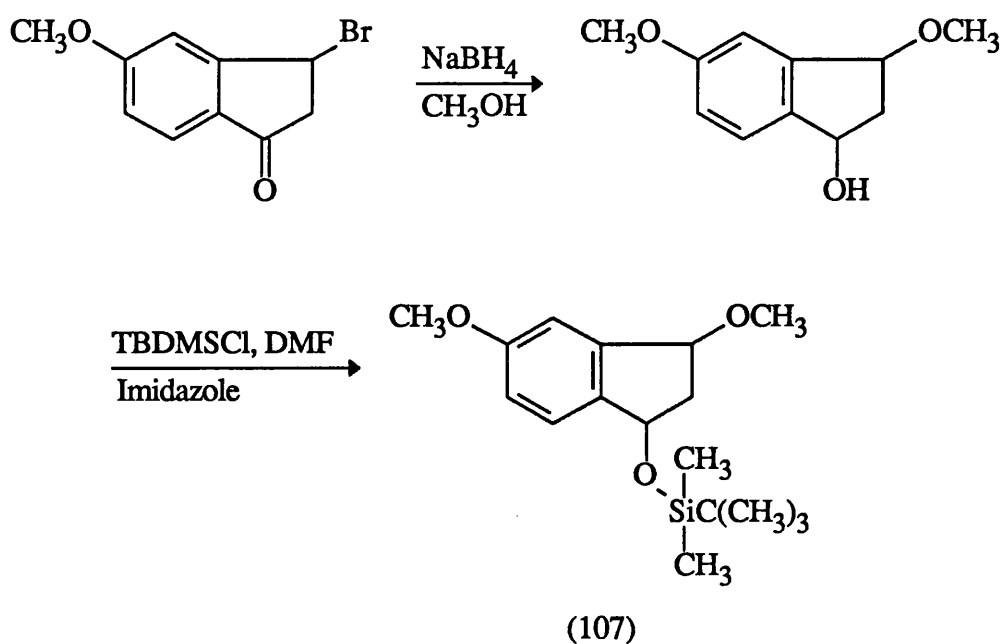
Clearly this approach was impractical for our purposes, and it is likely that the loss of reactivity of the indanone lies in the fact that its protonated form (106) is resonance stabilised thereby reducing its propensity to combine with potential nucleophiles, see scheme 22. House's isomer bears its methoxyl group *meta* to the carbonyl group where this type of conjugation is not possible.



Scheme 22.

Having belatedly recognised this problem we next turned to the reduction of the carbonyl group as a means of its protection. Treatment of the bromoindanone (83) with sodium borohydride in methanol produced a yellow oil showing a broad stretch at 3400 cm^{-1} in the infrared spectrum and an exchangeable broad 1 H singlet at δ 2.62 in the ^1H n.m.r. spectrum. Conversion of the indanol to its *t*-butyldimethylsilyl ether was

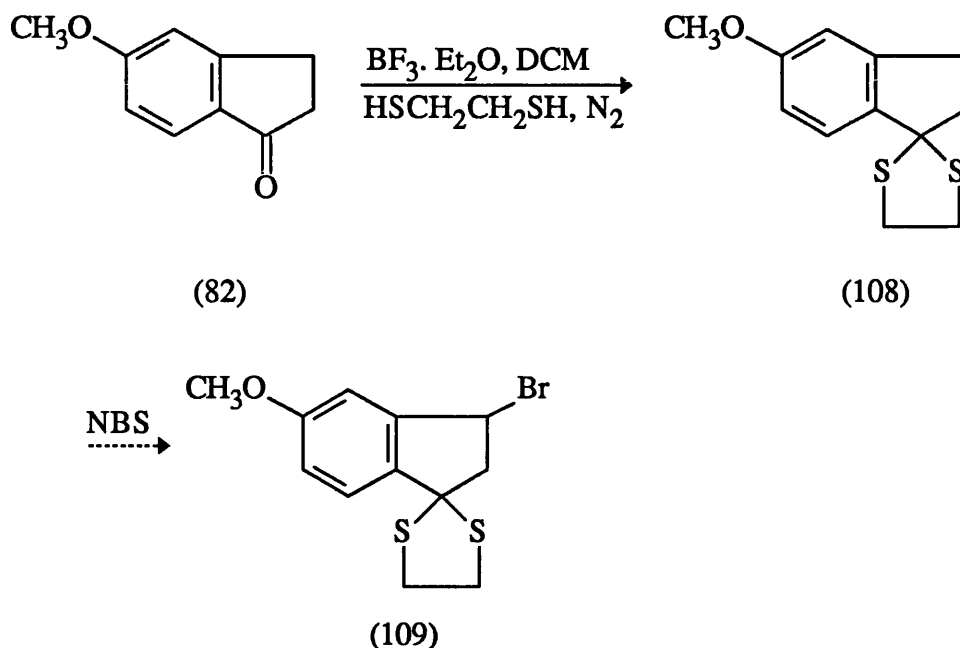
achieved using the standard conditions⁸⁰ affording an orange oil. However, although the ¹H n.m.r. spectrum of this product revealed the expected resonances due to the protons of the silyl group and the aromatic ring two 3 H singlets due to the protons of methoxyl groups were observed at δ 3.76 and δ 3.34. The first has the usual chemical shift of the aryl methoxyl group the other is compatible with a similar function bonded to the aliphatic unit. The mass spectrum indicated that the product did not contain bromine, but a molecular ion m/z 308 strongly supports the structural assignment (107). Other resonances in the ¹H n.m.r. spectrum (see experimental) also support this conclusion. It seems therefore that the bromine atom is substituted by a methoxyl group during the alkaline conditions of the first step (scheme 23).



Scheme 23.

A similar result was obtained if the reduction was performed in ethanol and now an ethoxyl group is inserted at C-3 instead of a methoxyl unit. Obviously we could have solved this problem by changing the solvent but since we were continually adding more steps to the synthesis we looked for an alternative means of protecting the ketone group at its own oxidation level. Indeed this was achieved quite simply since addition

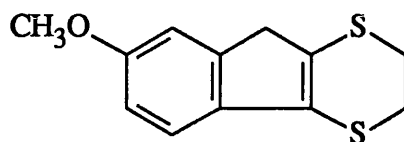
of boron trifluoride etherate to a mixture of the indanone (82) and 1,2-ethanedithiol in dry dichloromethane afforded the required 2-(5'-methoxy-1'-indanyl)-1,3-dithiolane (108) in 89 % yield (scheme 24).



Scheme 24.

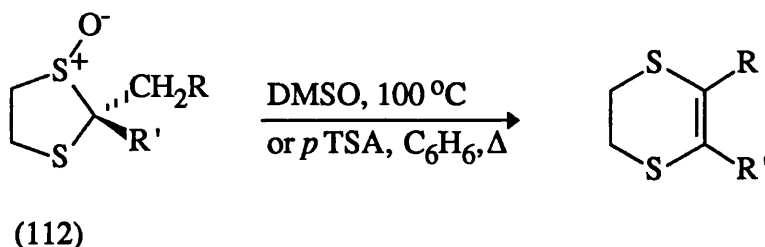
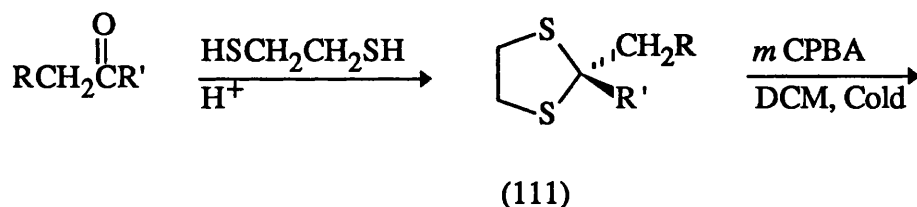
The dithiolane (108) was treated with *N*-bromosuccinimide and benzoyl peroxide in boiling carbon tetrachloride in the hope of producing 2-(3'-bromo-5'-methoxy-1'-indanyl)-1,3-dithiolane (109). A single product was obtained as a colourless solid which decomposed on standing after a number of weeks to a red gum. The ^1H n.m.r. spectrum of this compound, however, was a surprise since it consisted of the AMX spin - spin system of the aromatic ring protons and three singlets at δ 3.25, δ 3.40 and δ 3.78 integrating to four, two and three protons respectively. The ^{13}C n.m.r. spectrum shows a number of changes compared to the starting material, thus the resonances of the dithiolanyl ring are missing, instead a new triplet is present at δ 42.3 and the two triplets at δ 30.9 and δ 48.5 typical of the indanyl carbon atoms C-2 and C-3 are replaced by two new triplets at δ 26.0 and δ 27.2. Two new singlets also appear at δ 123.0 and δ 124.4. The mass spectrum gave no evidence that this

compound contains bromine and a molecular ion at m/z 236 was observed, indicating a molecular formula two mass units less than the starting material. This evidence is consistent with expansion of the dithiolane ring to a dithiin ring giving 6-methoxy-indanyl[2,3-*e*]-1,4-dithiin (110) as a likely structure.



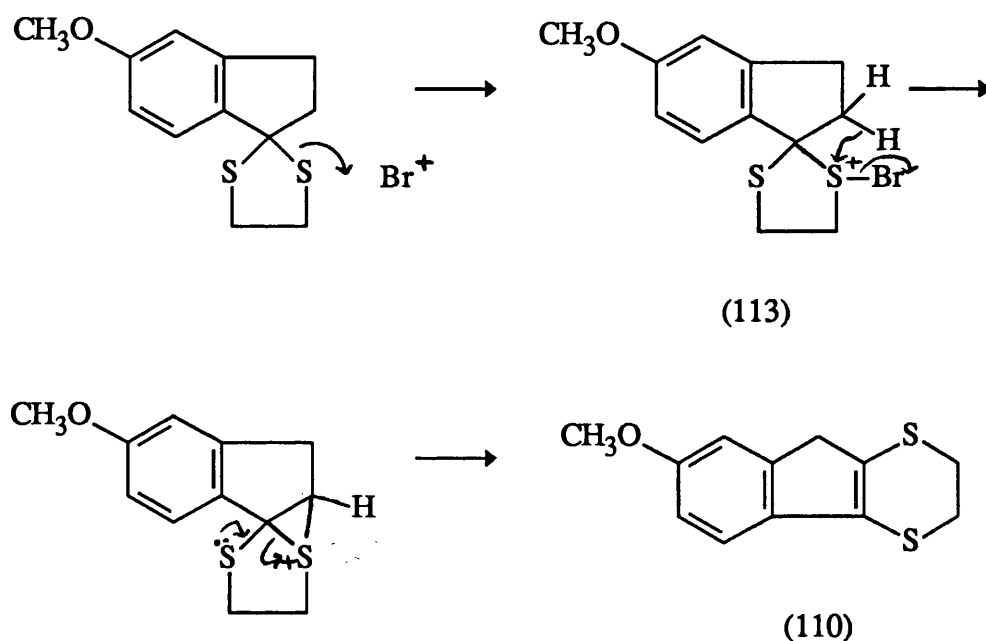
(110)

A search of the literature revealed that ring expansion of dithiolanes to dithianes is known. Chen ⁸¹ has found that oxidation of 1,3-dithiolane (111) with *meta*-chloroperbenzoic acid (*m*CPBA) can be controlled to give the mono sulphoxide (112), which can be rearranged thermally ^{81a} or under acid catalysis ^{81b} to the 5,6-dihydro-1,4-dithiin (113) (scheme 25).



Scheme 25.

Rubinstein and Wuethle⁸² have found that when an α -bromoketone is treated with 1,2-ethanedithiol and *p*TSA a 5,6-dihydro-1,4-dithiin is obtained in moderate yield. There is no mention of the rearrangement being achieved with *N*-bromosuccinimide and this would appear to be the most efficient conditions to achieve it. Since, under the conditions of the reaction, bromine radicals are generated, we thus suggest that our reaction occurs by the mechanism shown in scheme 26. Thus bromination of one of the sulphur atoms may generate a radical (113) as a result of opening of the dithiolane ring. Hydrogen atom abstraction quenches this radical and further abstraction with concomitant ring closure and bromine loss leads to the dihydrodithiin (110).



Scheme 26.

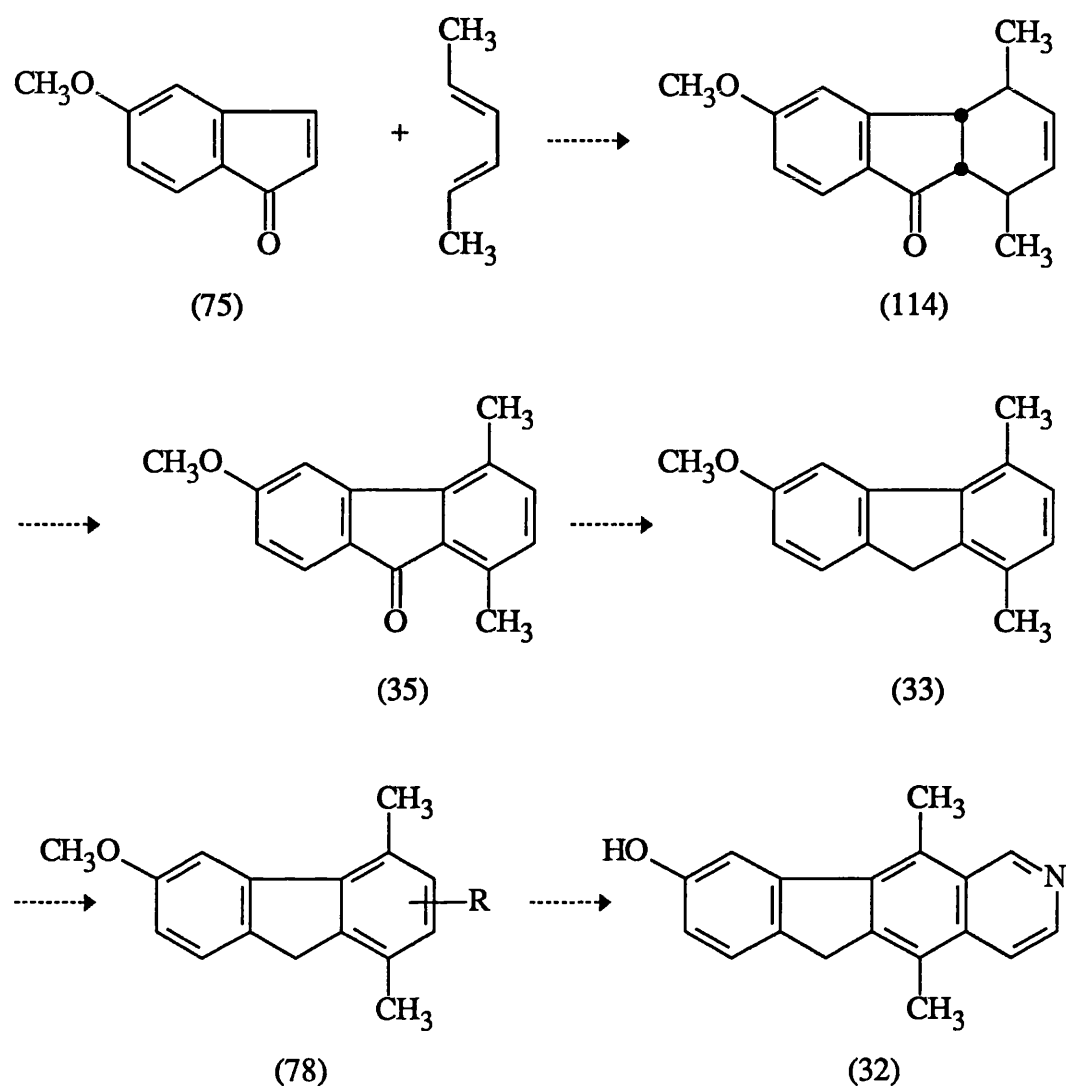
While producing an interesting result, this reaction was non-productive in terms of our objective, but as we had been successful in preparing the starting dithiolane (108) we reasoned that treatment of the bromoindanone (83) with 1,2-ethanedithiol and boron trifluoride etherate would give the required 2-(3'-bromo-5'-methoxy-1'-indanyl)-1,3-dithiolane (109). Reaction of the bromoindanone under the conditions used previously produced an orange gum. Thin layer chromatographic

analysis of this showed that the starting material ($R_F = 0.56$) had been consumed and that the gum contained predominantly one product ($R_F = 0.67$). Unfortunately chromatography of this compound under a variety of conditions simply led to its decomposition. An analysis of the ^1H n.m.r. spectrum of the crude product suggests that it is the desired 2-(3'-bromo-5'-methoxy-1'-indanyl)-1,3-dithiolane (109). The signal of the indanyl 3-H proton appears as a triplet ($J = 5$ Hz) at δ 5.3. The chemical shift of this resonance is thus in good agreement with the incorporation of a bromine atom at C-3. Since we were unable to purify this compound we pressed ahead to use it directly. Thus 3-ethylpyridine was treated with LDA / HMPT, as before, followed by the addition of the crude 2-(3'-bromo-5'-methoxy-1'-indanyl)-1,3-dithiolane. The products obtained from this reaction, however, proved to be recovered starting materials. At this stage, because of the pressures of time and our difficulty in preparing a suitably clean substrate for the anion reaction we decided to shelve our interest in this type of approach and to return to some of our earlier work.

We considered that a cycloaddition approach would still be viable, especially as we had demonstrated that 5-methoxy-1-indenone is capable of undergoing the Diels - Alder reaction. On reflection we decided that we had been rather ambitious in attempting to prepare a functionalised fluorenone, but that reaction with a simpler diene (*trans*-2-*trans*-4-hexadiene) would give an adduct that could be oxidised to the fluorenone (35). This could then be reduced to the fluorene (33) which could be further annulated to the desired target compound (scheme 27). Our first objective therefore was the formation of the adduct 6-methoxy-1,4-dimethyl-1,4,4a,9a-tetrahydro-9-fluorenone (114).

Heating 5-methoxy-1-indenone and *trans*-2-*trans*-4-hexadiene in boiling chloroform for 48 hours afforded, after chromatography, a pale yellow solid. An analysis of the ^1H n.m.r. spectrum of this product supports the view that it is indeed the adduct (114). Thus there are two 3 H doublets ($J = 7$ Hz) at δ 1.37 and δ 1.56 which indicate the presence of two CH_3CH units, with the supporting methine resonances as a broad multiplet at δ 2.45. The alkene protons, H-2 and H-3 appear as a

pair of double doublets of doublets ($J = 9, 3$ and 3 Hz) at δ 5.3 and δ 5.64 and the bridge protons at H-4a and H-9a resonate at δ 2.84 and δ 3.61 as double doublets ($J = 7$ and 7 Hz). The aromatic protons display the typical ABX spin - spin system.

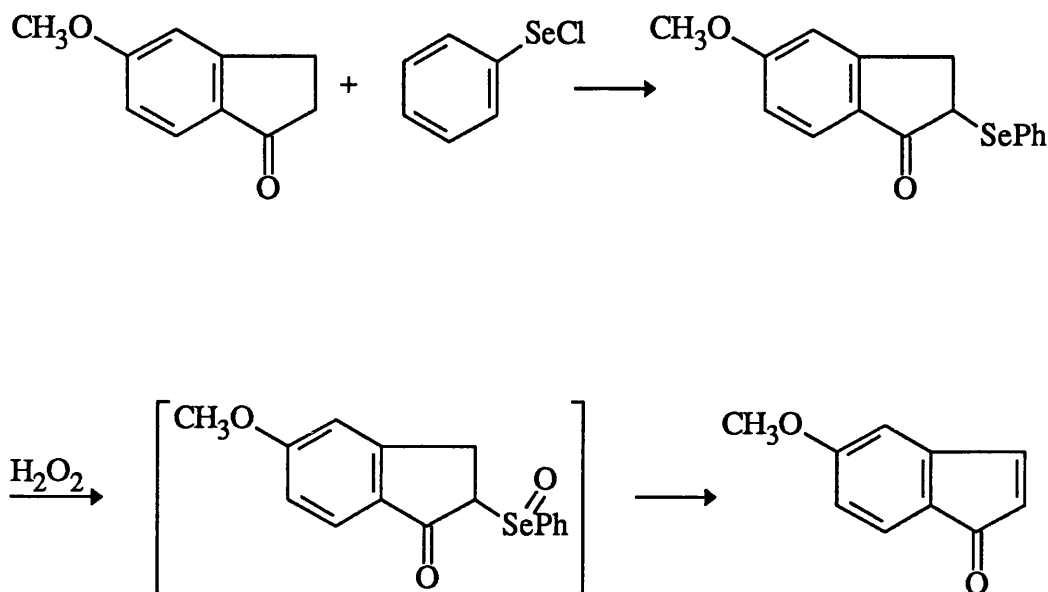


Scheme 27.

The yield of the adduct was only 49 %, but clearly at an early stage in the synthesis we were confident that this provided a base for further work. To succeed, however, we had two immediate requirements: the first was an efficient synthesis of our dienophile, 5-methoxy-1-indenone (75) and the second was to improve the yield of the Diels - Alder reaction.

As discussed earlier 5-methoxy-1-indenone (75) was prepared from 5-methoxy-1-indanone by allylic bromination followed by dehydrobromination with 2,4,6-collidine. The overall yield was 59 % but the bromination step is not clean and chromatography is needed to purify the bromocompound. The major problem lies in the second step which fails to go to completion and leads to a mixture of product indenone and bromoindanone. Both compounds have similar R_F values in various solvent systems which leads to a tiresome problem of separation, consequently yields of pure 5-methoxy-1-indenone are variable ranging from 20 % to 84 %. Because of these problems we set out to find a new procedure for the preparation of 5-methoxy-1-indenone.

“High potential” quinones are often used for dehydrogenations and in a model reaction 5,6-dimethoxy-1-indanone was heated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in boiling benzene. This resulted in the consumption of the starting material but did not yield 5,6-dimethoxy-1-indenone. Perhaps this is not too surprising since others⁸³ record that this type of dehydrogenation is not suitable for indanones. Selenoxide elimination has been used successfully in the preparation of α,β -unsaturated carbonyl compounds from their saturated counterparts.⁸⁴ Thus 5-methoxy-1-indanone was treated with phenylselenenyl chloride following Sharpless's conditions⁸⁴ and the resulting mixture treated with 30 % aqueous hydrogen peroxide. This gave 5-methoxy-1-indenone as the major product, after chromatography, in 35 % yield (scheme 28). While the indenone was isolated cleanly the yield was disappointing. Reich, Renga and Reich⁸⁵ have found that cyclic ketones having a hydrogen attached to the selenium bearing carbon are prone to competing side reactions. For example α -diketones have been isolated arising from the Pummerer reaction and when hydrogen peroxide is used as the oxidant the corresponding dicarboxylic acids are obtained.



Scheme 28.

In the light of these disappointments we decided to return again to the question of finding good conditions for the dehydrobromination of 3-bromo-5-methoxy-1-indanone. First we used pyridine (which is easier to remove than collidine) under the conditions used for the collidine reaction, but this resulted in the recovery of starting material. Pyridine is a weaker base than the alkylpyridines⁸⁶ and clearly in this case it is not strong enough to perform the reaction. Heating the bromoindanone with lithium bromide and lithium carbonate at 160 °C in dry *N,N*-dimethylformamide⁸⁷ resulted in a complex mixture, whereas vigorous stirring of the bromoindanone with finely divided calcium carbonate in *N,N*-dimethylacetamide at 120 °C achieved some dehydrobromination giving the desired indenone in 42 % yield. While pleased to find an alternative method of elimination we were concerned that the yield was only half that achieved with collidine and we were unable to significantly improve this by changing the reaction time or temperature.

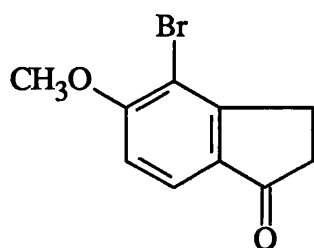
Diazabicyclo[5.4.0]undec-7-ene (DBU) has been used successfully in many dehydrohalogenation reactions⁸⁸ and indeed treatment of the bromoindanone (83) with this reagent in tetrahydrofuran at 0 °C resulted in the consumption of starting material. Unfortunately none of the desired 5-methoxy-1-indenone was obtained after work - up

and thin layer chromatography showed that a complex mixture had formed. The same result was obtained when the reaction was performed at -78 °C and the product allowed to warm to room temperature. Marvel and Hinman⁶² observed that 1-indenone polymerises rapidly under a number of conditions and DBU, its salts and quaternary salts have been used as catalysts in a large number of polymerisation processes.⁸⁹ Most probably this is also occurring here because if the DBU was added slowly during ten minutes and the reaction quenched immediately with dilute sulphuric acid the desired 5-methoxy-1-indenone was obtained cleanly in 85 % yield.

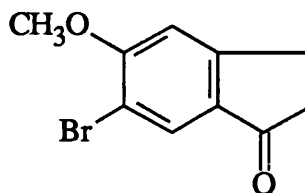
Because the free radical bromination of 5-methoxy-1-indanone produced a mixture of products we now turned towards an alternative means of functionalising the indanone. Friedrich and Tam⁶⁹ had prepared 2-bromo-5-methoxy-1-indanone, but were unable to effect elimination of hydrogen bromide from it by treatment with either lithium bromide / lithium carbonate in *N,N*-dimethylformamide or with 2,4,6-collidine. Since DBU is a much stronger base than collidine (pK_a in the region of 11.5⁸⁹) we thought that DBU might prove more effective. Friedrich and Tam prepared 2-bromo-5-methoxy-1-indanone using bromine in wet ether. In addition to the 2-bromoindanone required this also led to significant quantities of the 2,2-dibrominated product. Acid catalysed α -halogenation of ketones is a controllable process and it is easy to stop the reaction at the mono substitution point by controlling the addition of halogen.⁹⁰

In our hands addition of bromine to 5-methoxy-1-indanone in glacial acetic acid resulted in the formation of three products : 68 % recovery of the starting indanone and two new products in a 4:1 ratio. The mass spectra of each product showed molecular ion peaks at m/z 240 and 242 with an isotopic abundant ratio of 1:1 typical of the presence within the molecule of a bromine atom. However, the ¹H n.m.r. spectrum of these products showed the typical A₂B₂ spin - spin system of the indanyl protons at C-2 and C-3. Clearly the bromine atom must reside in the aryl ring, indeed the ¹H n.m.r. spectrum of the major isomer shows a pair of *ortho* coupled doublets at δ 6.95 and δ 7.75 ($J = 8$ Hz) indicating it to be 4-bromo-5-methoxy-1-indanone (115). Whereas the spectrum of the minor isomer shows two singlet peaks at δ 6.98 and

δ 7.95 suggesting this product to be 6-bromo-5-methoxy-1-indanone (116).

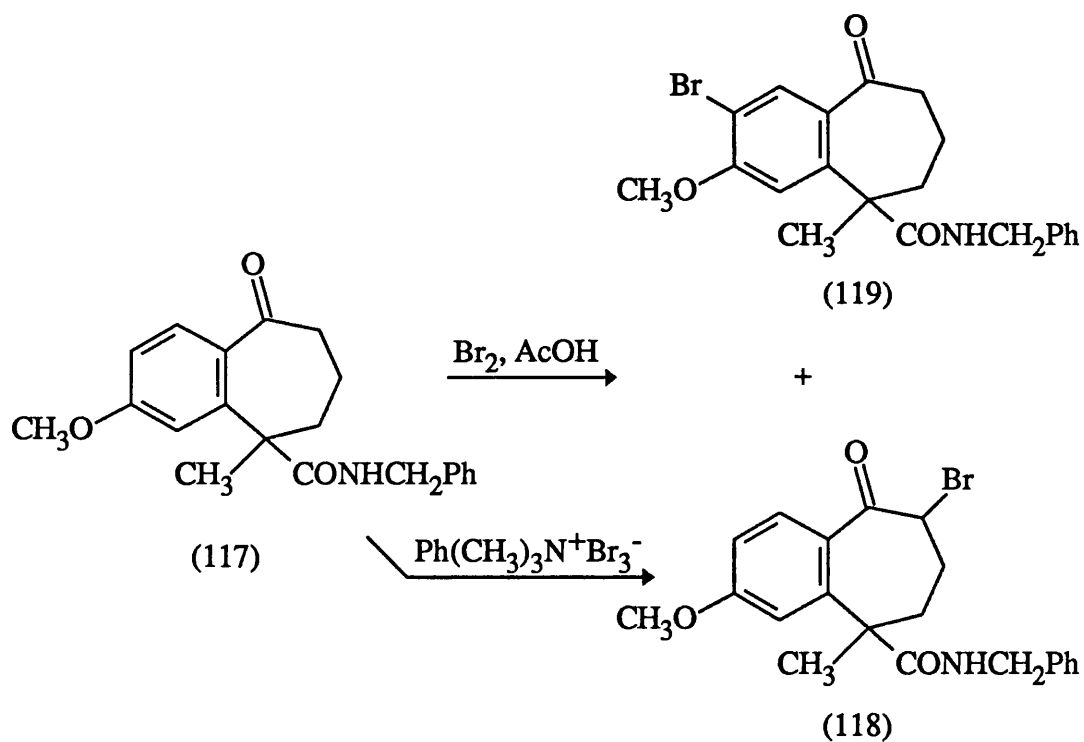


(115)



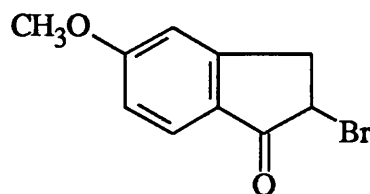
(116)

Recently Sedgeworth and Proctor⁹¹ found a similar result when attempting the bromination of the ketoamide (117). Thus a reaction with bromine in acetic acid resulted in a mixture of the desired bromoketoamide (118) and the unwanted isomer (119) (scheme 29). Interestingly treatment of the ketoamide (117) with phenyltrimethylammonium perbromide resulted in only the required isomer (118).



Scheme 29.

In our hands when 5-methoxy-1-indanone was treated with phenyltrimethylammonium perbromide in tetrahydrofuran following Sedgeworth and Proctor's conditions 2-bromo-5-methoxy-1-indanone (120) was obtained in 55 % yield.

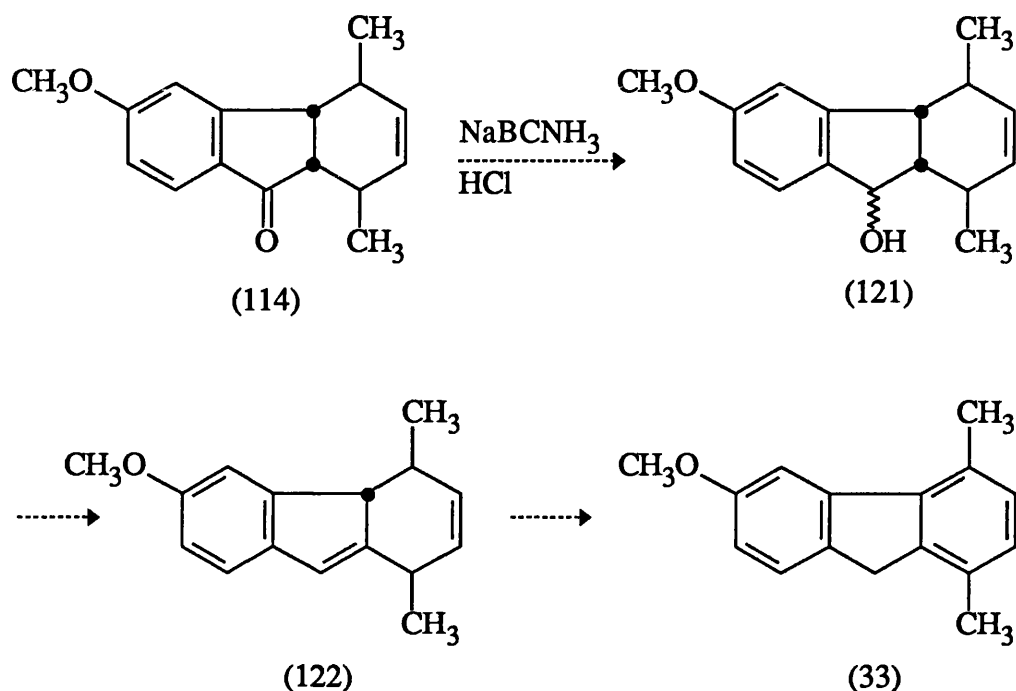


(120)

Reaction of this product with DBU, as before, resulted in the recovery of starting material. Clearly DBU is not basic enough to remove the benzylic proton, and in fact House and McDaniel ⁷⁹ achieve elimination using potassium t-butoxide. We did not follow this approach any further because the yield of 2-bromo-5-methoxy-1-indanone was poor when compared to our preparation of the 3-bromo isomer and, as the reaction failed to go to completion, we still had to resort to chromatography to isolate the product.

Having found a procedure for the preparation of clean 5-methoxy-1-indenone, we turned to the Diels - Alder reaction. The thermal reaction between 5-methoxy-1-indenone and *trans*-2-*trans*-4-hexadiene resulted in significant decomposition of the indenone as well as the formation of the adduct (114). We thought that Lewis acid catalysis might enable us to reduce the reaction time and temperature and hopefully reduce this decomposition. Reaction with zinc iodide as catalyst produced the adduct (114) in 64 % yield after five hours at 50 °C and 16 hours at room temperature. Pre-treatment of the 5-methoxy-1-indenone with boron trifluoride etherate at -78 °C followed by addition of *trans*-2-*trans*-4-hexadiene and allowing the reaction mixture to warm to room temperature resulted in the isolation of the adduct in 79 % yield. No decomposition of the indenone was observed under these conditions.

We thought that reduction of the adduct (114) with sodium cyanoborohydride at pH 3 would result in elimination of the product alcohol (121) to give the diene (122) with possible aromatisation to the fluorene (33) (scheme 30).

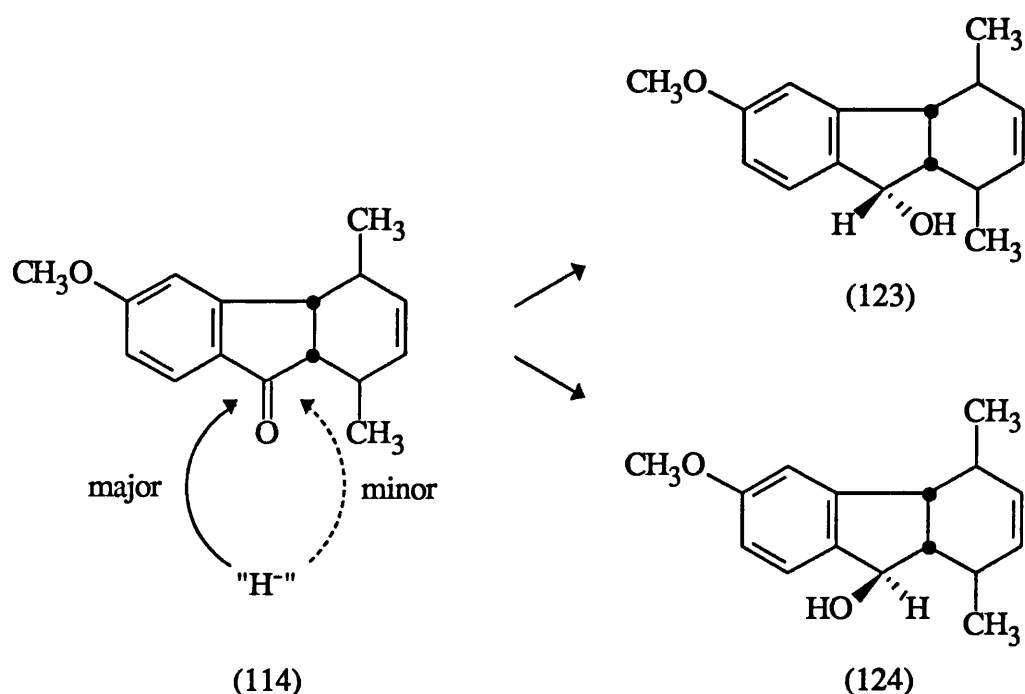


Scheme 30.

In the event reaction of the adduct (114) with sodium cyanoborohydride at pH 3 following standard conditions⁹² resulted in the recovery of starting material. Treatment of the adduct with lithium aluminium hydride resulted in the isolation of two products: the major product (71 %) was less polar than the starting ketone [$R_F = 0.58$, adduct (114) = 0.52] and the minor product (29 %) was more polar ($R_F = 0.33$).

The infrared spectrum of each product showed an absence of any carbonyl stretch (1685 cm^{-1} in the starting material), but contained sharp hydroxyl stretching bands at 3550 cm^{-1} (major product) and 3580 cm^{-1} (minor product). The more polar minor product also showed a broad peak at 3450 cm^{-1} indicating some degree of hydrogen bonding. The ^1H n.m.r. spectrum of each product shows the main features of the starting material (114), but includes some new signals in the hydroxyl region. The signal of the hydrogen atom of the hydroxyl group of the less polar product occurs

as an exchangeable doublet ($J = 10$ Hz) at δ 1.66, the resonance of H-9 appears as a double doublet ($J = 10$ and 7 Hz) at δ 4.93. However, for the more polar product the hydroxyl signal is shifted downfield and occurs as an exchangeable singlet at δ 1.86, whereas the shift of the H-9 resonance remains constant but now gives rise to a doublet ($J = 6$ Hz). This downfield shift is in line with hydrogen bonding in the hydroxyl group of this product. Clearly these products are the isomeric alcohols (123) and (124) and a likely explanation for these phenomena is that the hydroxyl group of the major, less polar, isomer (123) is in a hindered environment. This makes it less available for hydrogen bonding and also slows down the rate of exchange so that coupling is observed between the H-9 and the hydroxyl proton. The reverse is true for the minor, more polar, isomer (124) with the hydroxyl group open and thus available for hydrogen bonding and more rapid exchange. The formation of the major isomer (123) is consistent with delivery of hydride from the less hindered side of the adduct (114) as shown in scheme 31.

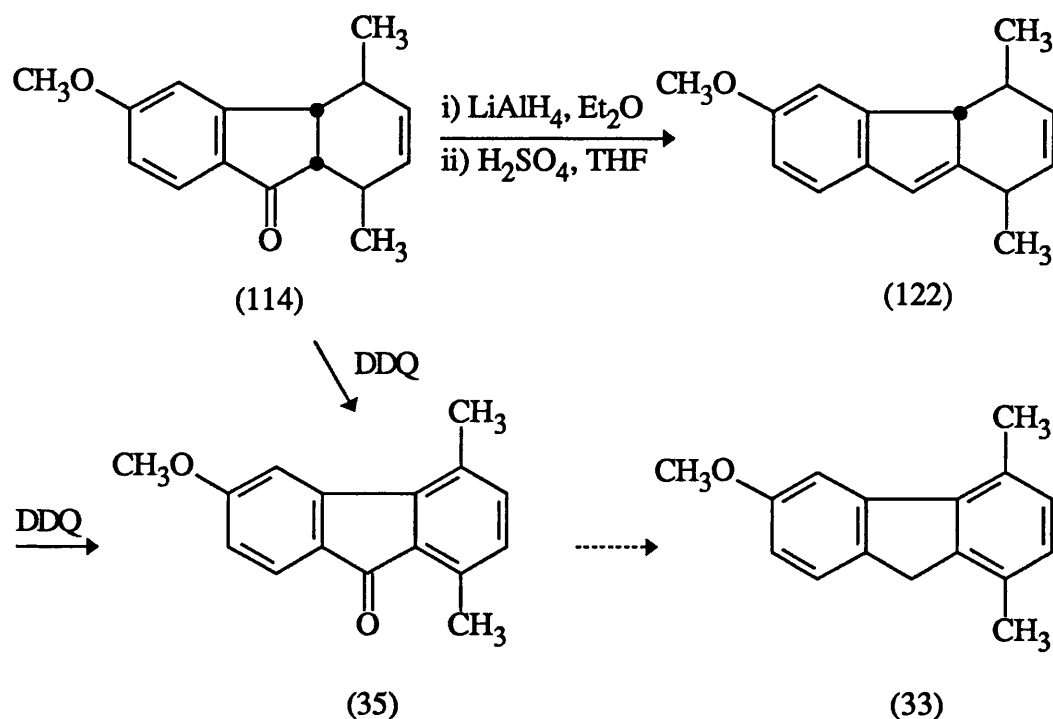


Scheme 31.

The same result was obtained when the adduct (114) was heated with sodium borohydride in wet methanol under reflux. Reaction at room temperature failed to achieve any significant reduction after 24 hours. Since the sodium cyanoborohydride reduction was performed at room temperature it would be reasonable to expect the reaction to proceed at higher temperatures, although this was not attempted.

Both isomeric alcohols could be converted to 6-methoxy-1,4-dimethyl-4,4a-dihydro-1*H*-fluorene (122) by heating with 5 M sulphuric acid in tetrahydrofuran. We considered that the diene should be fairly easily oxidised and isomerised to give the desired fluorene (33). Treatment of the diene (122) with DDQ resulted in the isolation of 6-methoxy-1,4-dimethyl-9-fluorenone (35) in 36 % yield as the sole product. We were initially confused by the melting point of this product at 144 - 5 °C as the literature ⁴¹ quotes its m.p. as 125 - 6 °C and states that it has a carbonyl stretching band of 1760 cm⁻¹ in the infrared spectrum while we find a carbonyl absorption at 1690 cm⁻¹. Our sample does afford a satisfactory elemental analysis and its ¹H n.m.r. spectrum is in close agreement with the data described in the literature.

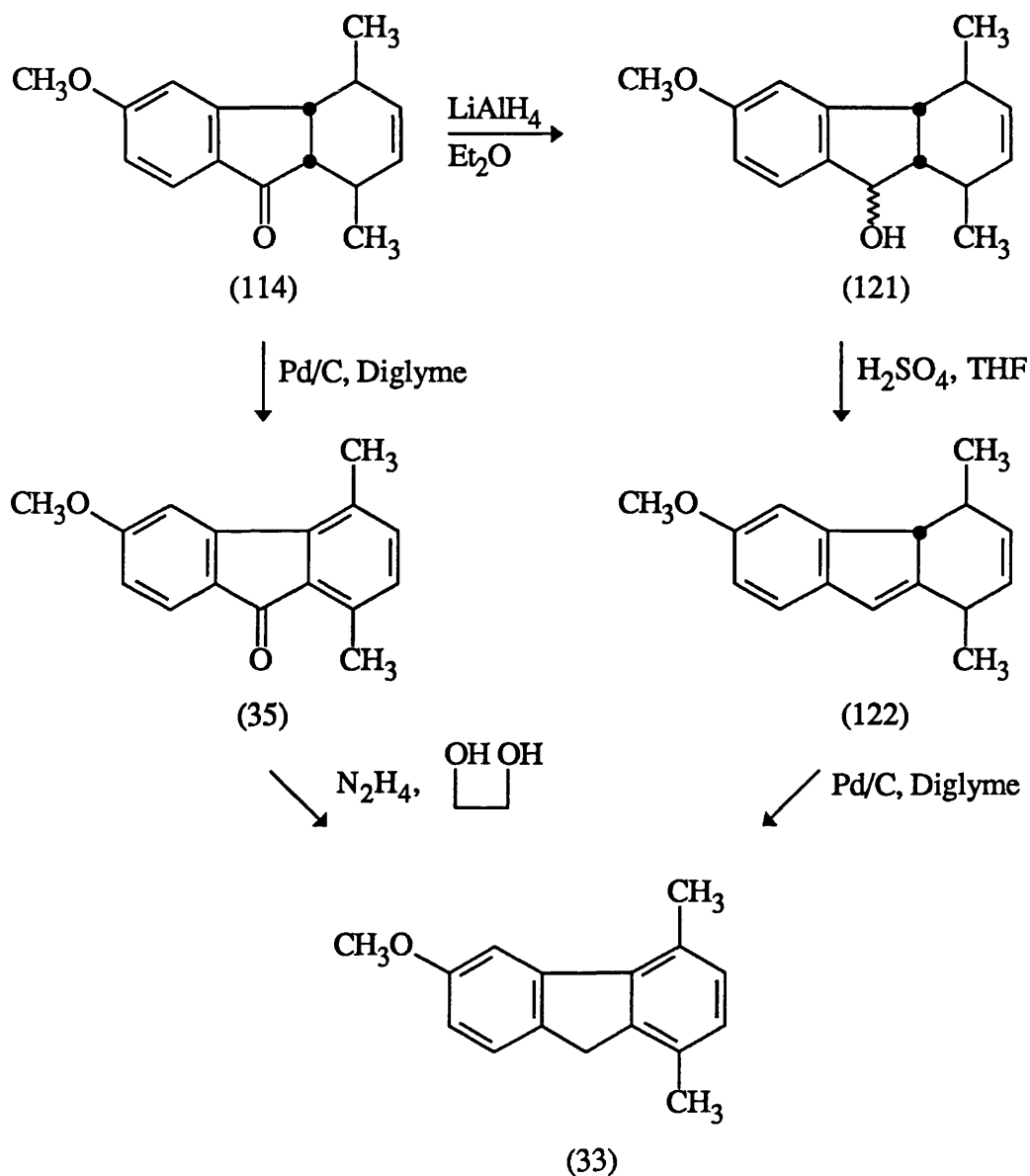
As we had achieved over oxidation in this case we considered that reaction of the Diels - Alder adduct (114) with DDQ should take us directly to the fluorenone (35) without the need for reduction, elimination and oxidation. DDQ has been used previously in the aromatisation of Diels - Alder adducts. ⁹³ Heating the adduct (114) with DDQ in boiling benzene produced the desired fluorenone (35) in 51 % yield (scheme 32).



Scheme 32.

A search of the literature showed that Harris, White and McNeil ⁹⁴ had prepared $[\text{9-}^{14}\text{C}]$ fluorene from the corresponding $[\text{9-}^{14}\text{C}]$ fluorenone under Wolff - Kishner conditions, but without the need for added base. 6-Methoxy-1,4-dimethyl-9-fluorenone was next reacted under these conditions. Thus heating it with 99 % hydrazine hydrate under reflux in 1,2-ethanediol for four hours afforded the desired 6-methoxy-1,4-dimethylfluorene (33) in 73 % yield. We felt that the aromatisation was still rather unsatisfactory and in an attempt to improve the productivity the adduct was heated with 10 % palladium on carbon. This worked well and gave 6-methoxy-1,4-dimethyl-9-fluorenone (35) in 85 % yield. In further work a second product 6-methoxy-1,4-dimethylfluorene (33) was isolated in 15 % yield, showing that unless all the hydrogen is removed from the reaction mixture by flushing with an inert gas, such as nitrogen, reduction of the substrate may also occur, leading perhaps first to the alcohol (121) which then dehydrates and aromatises (see scheme 33).

Support for this comes from the fact that later when a sample of the diene (122) was heated with palladium on carbon suspended in diglyme the fluorene (33) was obtained in good yield.



Scheme 33.

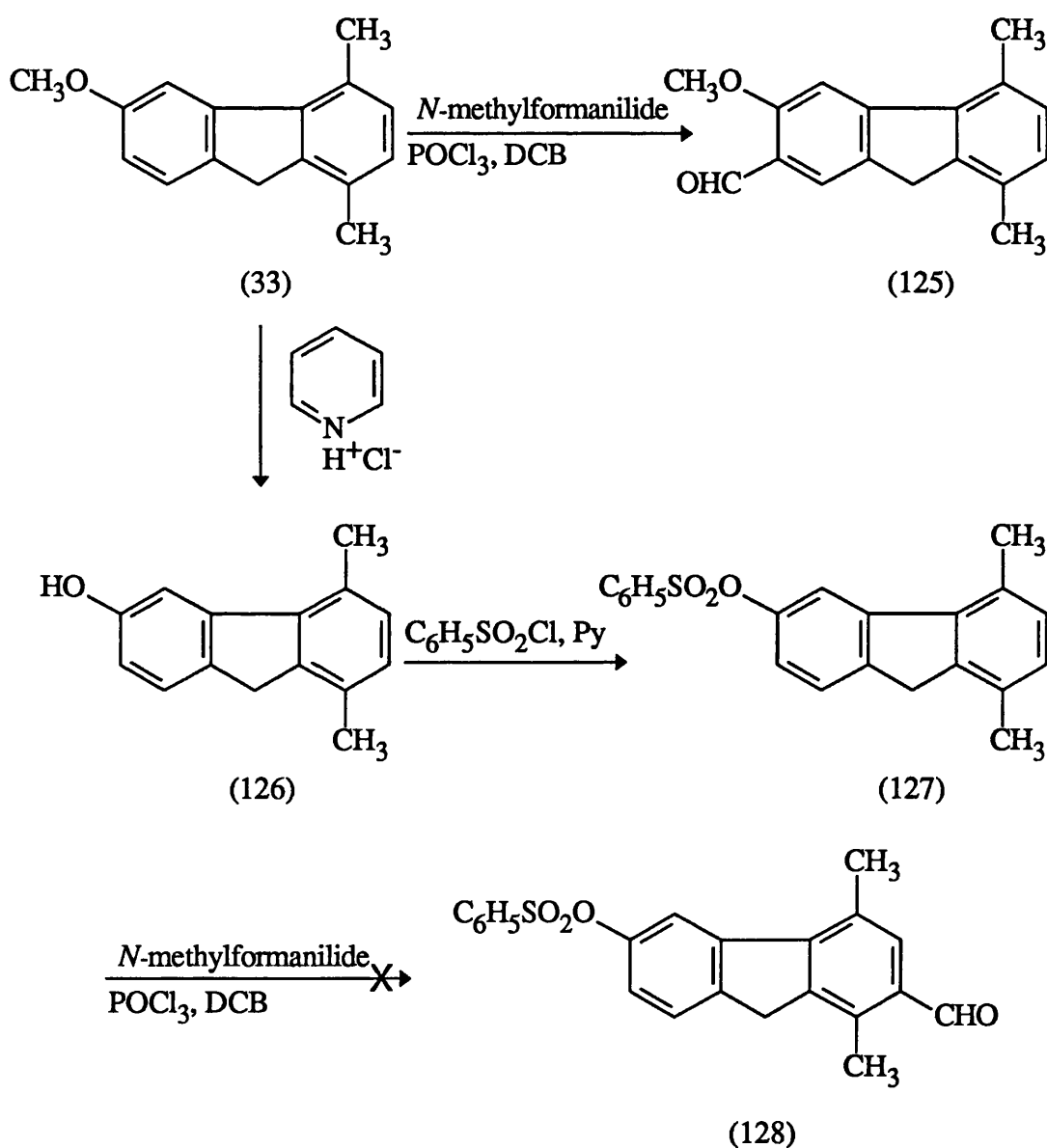
The three step process; reduction, elimination and aromatisation resulted in the isolation of the fluorene (33) in 86 % overall yield. This compares very favourably with the 61 % overall yield obtained for the aromatisation, Wolff - Kishner reduction approach as outlined above.

We now had a good, reliable synthesis of 6-methoxy-1,4-dimethylfluorene (33) and we next required a means of selectively functionalising the molecule to enable annulation of the final pyridine ring. Treatment of the fluorene with phosphorus oxychloride, *N,N*-dimethylformamide complex ⁹⁵ resulted in the recovery of unchanged starting material. Changing to the reagents *N*-methylformanilide and phosphorus oxychloride ⁹⁶ and using 1,2-dichlorobenzene as solvent at a reaction temperature of 90 °C resulted in a 74 % recovery of 6-methoxy-1,4-dimethylfluorene plus a single new product. This product showed a carbonyl stretching band at 1665 cm⁻¹ in its infrared spectrum as expected for an aromatic aldehyde. The ¹H n.m.r. spectrum shows eight singlets: In addition to those originating from the resonances of the two methyl protons and those of the 9-methylene and 6-methoxy groups of the fluorene nucleus, a 2 H singlet at δ 7.05 due to the aryl protons H-2 and H-3 is observed. The usual ABX spin - spin system due to the protons of the A-ring are absent and is replaced by two 1 H singlets at δ 7.3 and δ 7.85 due to H-5 and H-8. The aldehyde proton resonates at δ 10.48. These changes to the spectrum of the fluorene (33) indicate that the new product is 6-methoxy-1,4-dimethylfluorene-7-carbaldehyde (125).

This result indicates that the methoxyl group present in ring-A has a greater activational effect than the two methyl substituents of ring-C and to overcome this difficulty it was necessary to replace the electron donating methoxyl function by an *O*-benzenesulphonyl unit.

Treatment of 6-methoxy-1,4-dimethylfluorene with iodotrimethylsilane ⁹⁷ in chloroform at 55 °C for 22 hours resulted in the isolation of 6-hydroxy-1,4-dimethylfluorene (126) in 9 % yield. This result was disappointing, but Jung and Lister note that aryl - alkyl ethers are only cleaved slowly by this procedure. Fortunately fusion of the fluorene (33) with pyridinium hydrochloride ⁹⁸ at 220 °C for two hours afforded, after work - up, the desired hydroxyfluorene (126) in apparently good yield and this was used without purification. Reaction of this product with benzenesulphonyl chloride in pyridine afforded the desired 1,4-dimethyl-6-phenylsulphonyloxyfluorene (127) in

75 % yield from the starting methoxyfluorene (scheme 34). The infrared spectrum shows no hydroxyl absorption band, but has two strong bands at 1365 and 1140 cm^{-1} which correspond to stretching bands of the sulphonyloxy group. Unfortunately reaction of the 1,4-dimethyl-6-phenylsulphonyloxyfluorene (127) under the previously successful Vilsmeier - Haack ⁹⁶ reaction conditions failed to produce any 1,4-dimethyl-6-phenylsulphonyloxyfluorene-2-carbaldehyde (128) even after an extended reaction time (scheme 34).



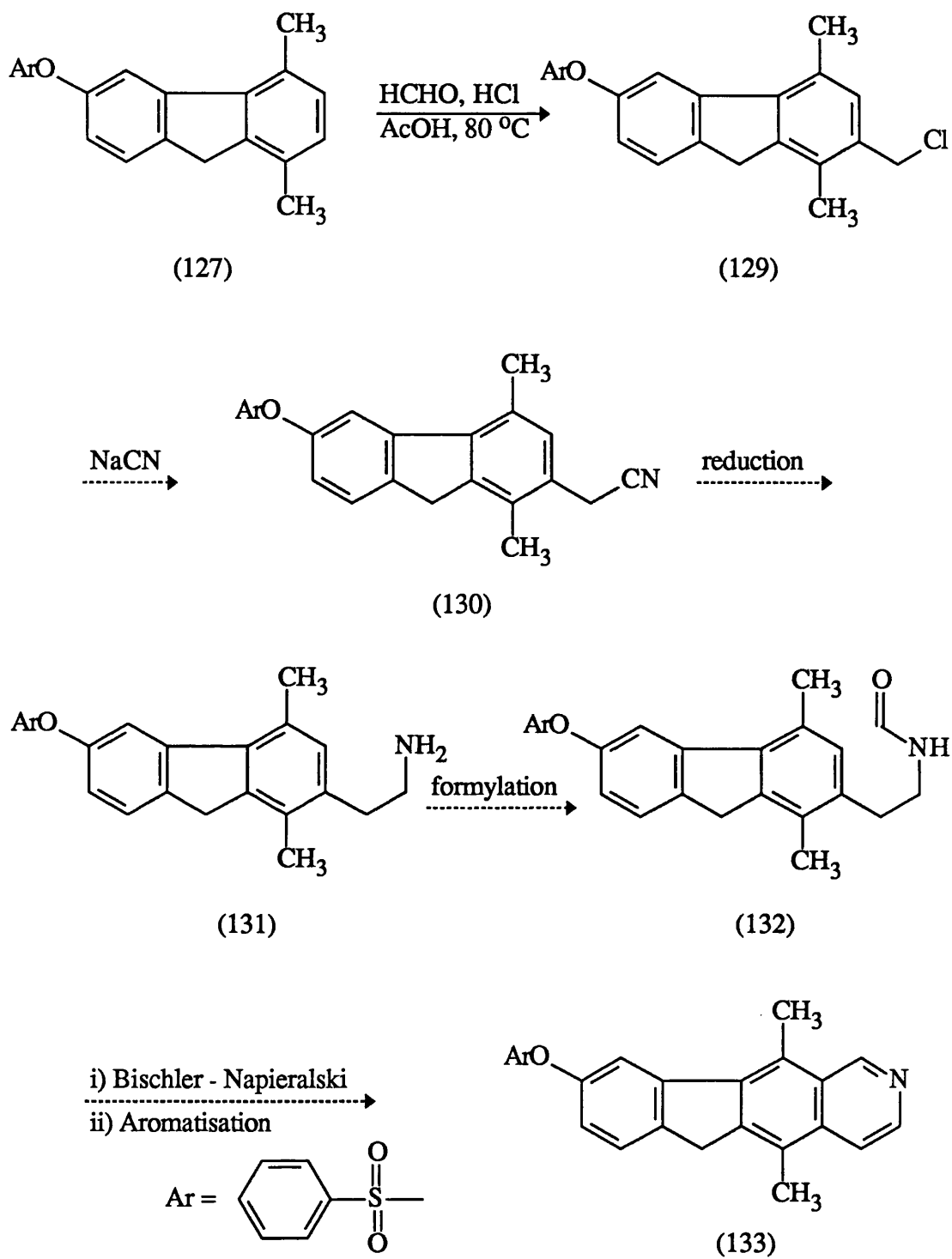
Scheme 34.

The Vilsmeier - Haack reaction is only successful with reactive aromatic substrates and fails to react with benzene and the alkylbenzenes.⁹⁹ Clearly our substrate is now an insufficiently reactive substrate for this reaction. However, chloromethylation is a much easier process and reacts with benzene and the alkylbenzenes to give chloromethylated products in good yield.¹⁰⁰

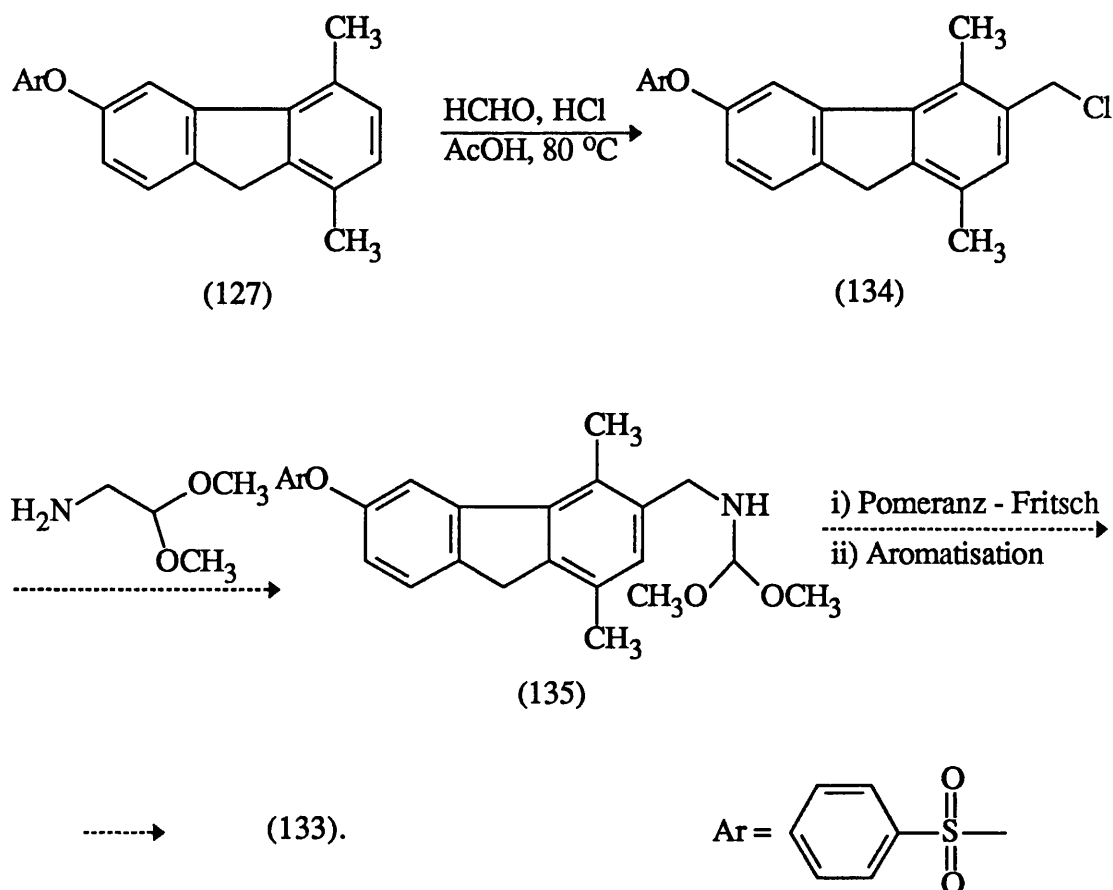
Therefore we reacted our substrate with 40 % aqueous formaldehyde and concentrated hydrochloric acid in glacial acetic acid at 80 °C. Work - up after 4-5 hours afforded a chloromethylated product in 91 % yield. From the ¹H n.m.r. spectrum of this compound we could determine that one chloromethyl unit had been incorporated. For example, a 2 H singlet at δ 4.65 is observed. Moreover the nature of the aryl proton resonances clearly shows that the unit is attached to ring-C. The ABX spin - spin system of the A-ring resonances are still present whereas the usual 2 H singlet due to the resonances of H-2 and H-3 at δ 6.99 is now reduced to a 1 H signal at δ 7.07. The usual type of analysis of transition states for predicting the orientation of electrophilic substitution indicates C-2 to be the preferred reaction site, but this is slim evidence on which to proceed with the rest of the synthesis since the direction needed to form ring-D from a substituent at C-2 differs from that starting from C-3.

Thus assuming that we had prepared the 2-chloromethylfluorene (129) we would need to displace the halogen atom with cyanide ion to give the cyanomethylfluorene (130). Reduction of this compound would give the amine (131), formylation of which would lead to the formamide (132) a substrate for a Bischler - Napieralski ring closure. Finally aromatisation of the product from this last reaction would afford our protected target molecule (133) (scheme 35).

If we had obtained the 3-chloromethylfluorene (134) we would need to elaborate the chloromethyl substituent to give the acetal (135) which through a modified Pomeranz - Fritsch cyclisation might afford the required pyridofluorene (scheme 36).



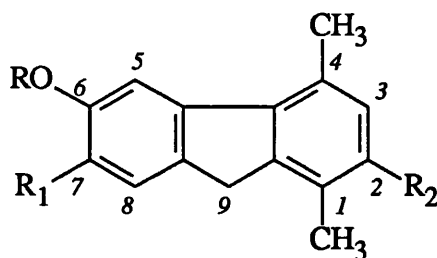
Scheme 35.



Scheme 36.

We had intended to confirm the identity of our product by the use of the nuclear Overhauser effect (n.O.e.). For this purpose our reference points were to be the resonances of the two aromatic methyl proton singlets. However, the ^1H n.m.r. spectrum of the chloromethyl compound posed a problem in that the resonances of the two methyl group protons had similar chemical shifts and occur at δ 2.38 and δ 2.39, thus making any n.O.e. experiments impossible. As can be seen from table 2 changing the 6-oxygen functionality from methyl to benzenesulphonyl causes a major upfield shift in one of the methyl resonances from δ 2.64 to δ 2.37. Whereas the other methyl signal remains relatively unaffected.

THE CHEMICAL SHIFT OF THE METHYL GROUP PROTONS ON C-1 AND C-4.



SUBSTITUENT.	1-CH ₃ .	4-CH ₃ .
R = CH ₃ , R ₁ = R ₂ = H	2.32	2.64
R = CH ₃ , R ₁ = CHO, R ₂ = H	2.28	2.61
R = R ₁ = R ₂ = H	2.35	2.65
R = PhSO ₂ , R ₁ = R ₂ = H	2.30	2.37
R = PhSO ₂ , R ₁ = H, R ₂ = CH ₂ Cl	2.38	2.39
R = PhSO ₂ , R ₁ = H, R ₂ = CH ₂ CN	2.27	2.36

Table 2.

The methyl signal most likely to have been shifted is that attached to C-4 since models indicate that it may lie in the shielding zone created by the benzenesulphonyloxy substituent at C-6. The insertion of the chloromethyl unit causes a minor downfield shift which has the effect of bringing the two methyl proton resonances almost to the same chemical shift.

This last change also points towards substitution at C-2 but once again this view is far from conclusive. The ¹³C n.m.r. spectrum is unhelpful in this case because in each of the model compounds listed in the table it is not possible to assign the carbon atom resonances with absolute certainty, based on calculations from model systems. 101

Despite this problem we decided to work on the assumption that we had prepared the 2-chloromethyl isomer (129) and to prepare 2-cyanomethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (130). We reasoned that with the removal of the inductive effect of the chlorine atom the ^1H n.m.r. spectrum might revert and allow the type of analysis we originally sought.

Treatment of 2-chloromethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (129) with sodium cyanide in dimethyl sulphoxide (DMSO) at 90 °C, following the conditions of Smiley and Arnold ¹⁰² afforded the desired 2-cyanomethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (130) in 60 % yield. The infrared spectrum of this product showed a sharp stretching band at 2250 cm^{-1} corresponding to the presence of a nitrile group, whereas the ^1H n.m.r. spectrum showed the usual aromatic proton signals. Most usefully the chemical shifts of the two methyl proton signals had indeed changed position to δ 2.27 and δ 2.36 as expected. However, most unfortunately the benzylic methylene proton resonance had shifted upfield from δ 4.65 in the chloromethylfluorene (129) to δ 3.67 in this case. This resonance is now very close to the 9- CH_2 proton signal at δ 3.63.

Nevertheless we decided that a nuclear Overhauser difference experiment might be possible and the results are as outlined in Figure 1.

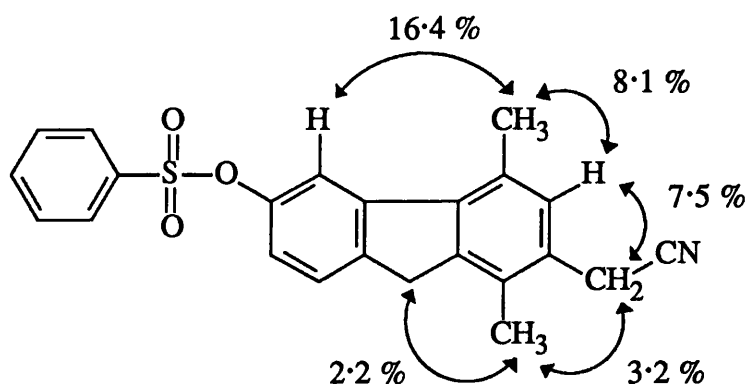
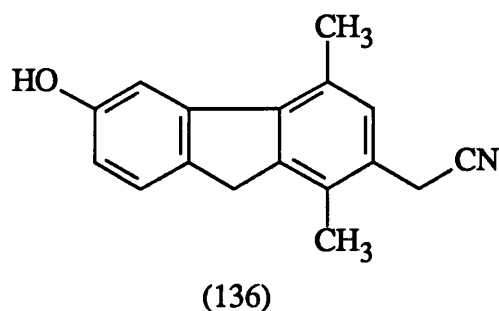


Figure 1.

Thus irradiation at δ 3.6 resulted in an enhancement of the C-1 methyl proton resonance at δ 2.27 by 3.2 % and also gave rise to a 7.5 % enhancement of the H-3 proton resonance at δ 7.07. Irradiation of the C-4 methyl proton signal at δ 2.36 produced an enhancement of the signal of H-3 by 8.1 %, and a 16.4 % enhancement of that at H-5 (δ 7.24). These results indicate the mutual proximity of all the protons involved. Irradiation of the other methyl proton resonance at δ 2.27 caused a 3.2 % enhancement of the other methylene protons (possibly of the cyanomethyl group) at δ 3.67 and a 2.2 % enhancement of the other methylene proton singlet at δ 3.63.

These results provided good support for the formation of the 2-substituted compound (130). While this work was in progress a single crystal X ray experiment was performed on the 2-chloromethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (129). The computer generated structure is shown in figure 2 and this fully confirms the regiochemistry of the substitution reaction.

With this support we were able to press on towards our target and utilise the Bischler - Napieralski ring closure process as outlined in scheme 35. Although we had synthesised the nitrile (130) already the yield was only 60 %. The conditions used in the formation of this product required heating the chloromethyl compound with sodium cyanide in DMSO at 90 °C. Under these conditions some de-*O*-sulphonylation occurs and the phenol (136) produced was lost during work - up. By reducing the severity of the conditions to a similar reaction now at room temperature the nitrile was formed in 90 % yield within 30 minutes.



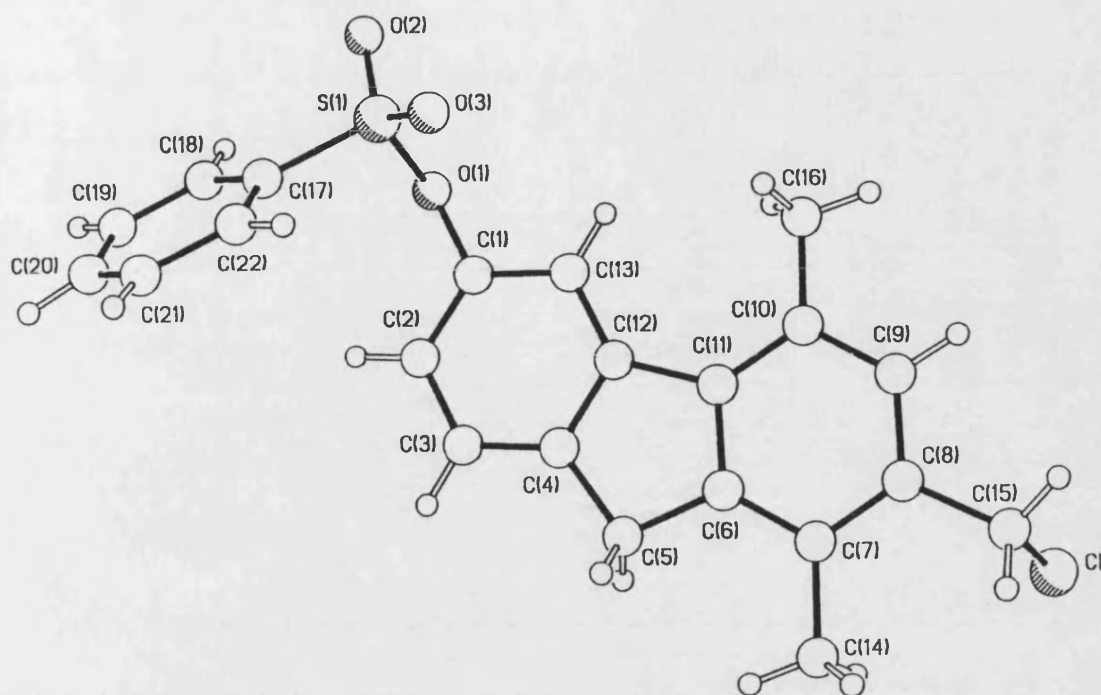
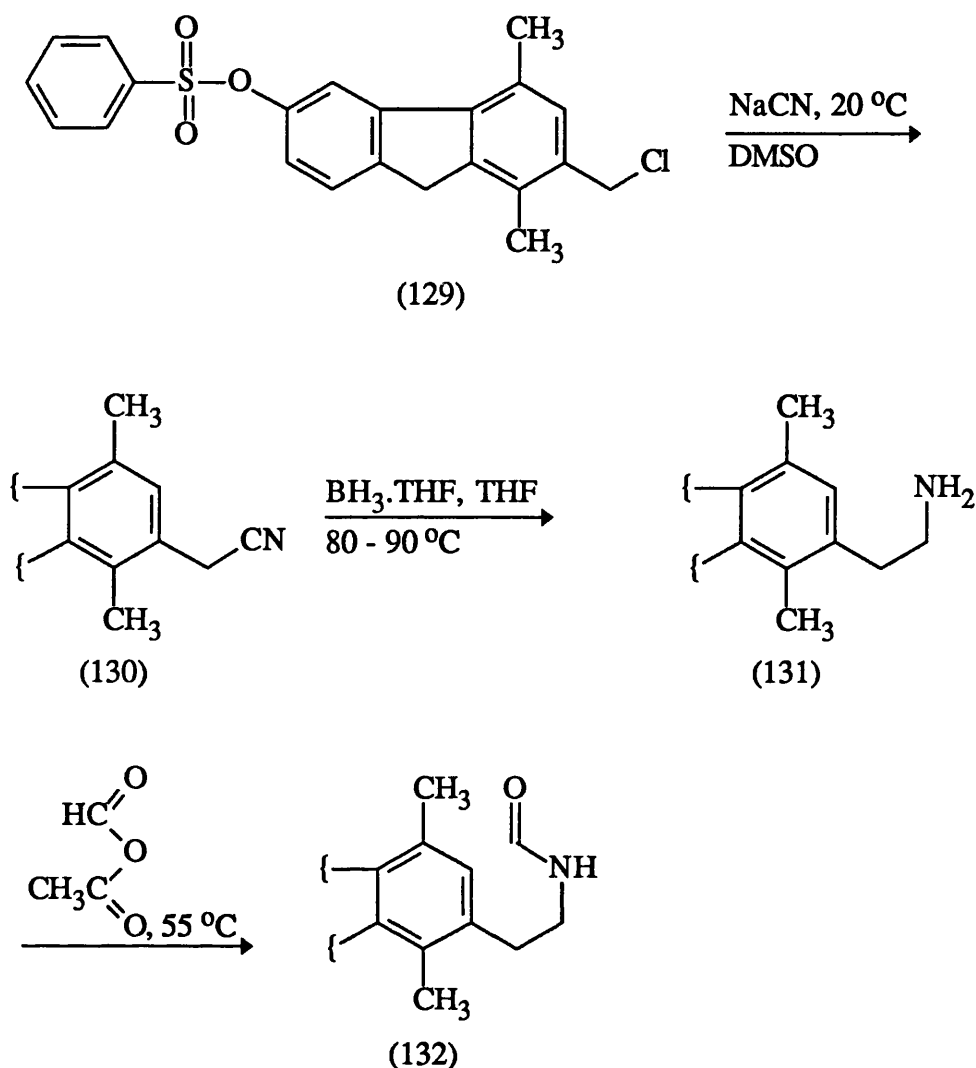


Figure 2.

Lithium aluminium hydride has been used successfully in the reduction of nitriles to primary amines.¹⁰³ Treatment of 2-cyanomethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (130) with lithium aluminium hydride in boiling tetrahydrofuran consumed the starting nitrile, however, the resulting product proved to be an intractable brown solid and this approach was not repeated. Instead we turned to diborane which has also been shown to reduce nitriles to amines.¹⁰⁴ Heating the nitrile with borane-tetrahydrofuran complex in tetrahydrofuran at 80 - 90 °C for 24 hours produced the desired 2-(2-aminoethyl)-1,4-dimethyl-6-phenylsulphonyloxyfluorene (131) in 56 % isolated yield (scheme 37). The infrared spectrum shows a loss of the nitrile stretching band and the presence of -NH₂ absorptions at 3360 and 3200 cm⁻¹.

N-formylation of this compound by treatment with formic - acetic anhydride¹⁰⁵ at 55 °C for 1.5 hours gave the amide (132) in 82 % yield.



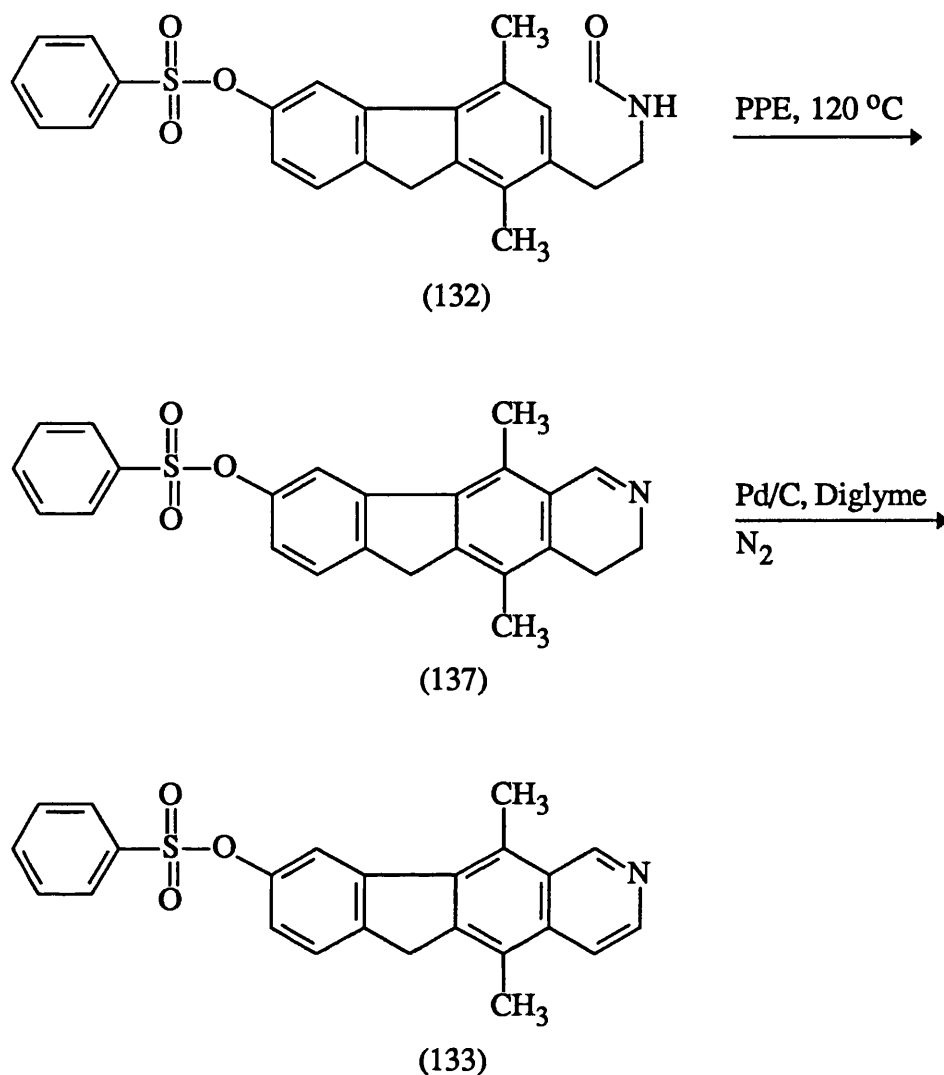
Scheme 37.

Successful Bischler - Napieralski cyclodehydration reactions normally require an electron rich aromatic ring,¹⁰⁶ but in our case the substrate (132) is not particularly activated towards electrophilic attack. Accordingly we selected phosphorus pentoxide as our dehydrating agent since this reagent is frequently employed in difficult cases.¹⁰⁶ Unfortunately even this reagent was inappropriate and even after heating the amide with a large excess of phosphorus pentoxide in boiling toluene for many hours no reaction was observed. A more convenient reagent is phosphorus oxychloride, but with this in toluene at reflux a black tar gradually formed. Lower boiling point solvents like

chloroform were also tried, but this also caused tar formation.

Phosphorus pentachloride has been used in cases where phosphorus pentoxide has failed, ¹⁰⁷ but with our substrate, reaction at room temperature in chloroform did not produce any tangible products and only when the reaction mixture was heated under reflux was the starting material consumed. However, on work - up only a multicomponent gum was obtained.

Dixit, Khanna and Anand ³⁹ in their synthesis of the parent tetracycle 5,11-dimethyl-6*H*-pyrido[4,3-*b*]fluorene (21) cyclised 2-(2-formamidoethyl)-1,4-dimethylfluorene (30) through reaction with "super polyphosphoric acid" at a temperature of 170 °C. Similarly Kanaoka, Sato, Yonemitsu and Ban ¹⁰⁸ have shown that ethyl polyphosphate is useful in the Bischler - Napieralski reaction, but when we heated our substrate (132) with neat ethyl polyphosphate at 180 °C only a tar formed. The same result was obtained when the reaction was performed at 150 °C instead of 180 °C. However, no reaction occurred when the reaction was performed either at reflux in chloroform or without solvent at 100 °C. Finally treatment of the substrate (132) with ethyl polyphosphate at 120 °C for one hour resulted in the isolation of a red oil (λ_{max} 260nm). The infrared spectrum of this oil shows no -NH or carbonyl bands, but does exhibit aromatic stretching frequencies at 1600 and 1580 cm⁻¹, plus S-O stretching bands at 1370 and 1145 cm⁻¹. This oil was reacted immediately with 10 % palladium on carbon in boiling diglyme and on work - up a yellow oil was obtained in low yield. It has λ_{max} 270 nm indicating a small increase in conjugation in this molecule relative to the parent.



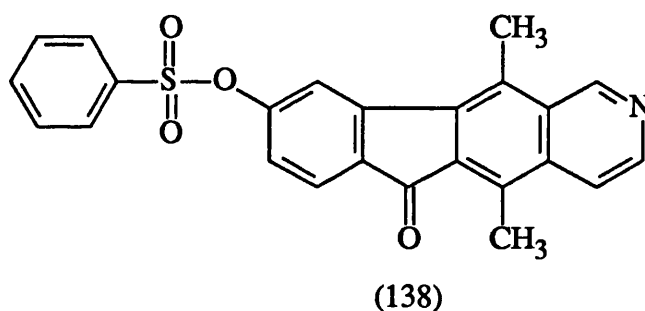
Scheme 38.

The ¹H n.m.r. spectrum substantiates this view and in particular now shows two extra methine resonances as doublets ($J = 6$ Hz) at δ 7.78 (H-4) and δ 8.60 (H-3). These chemical shifts are compatible with similar values obtained for 6*H*-pyrido-[4,3-*b*]carbazoles,¹⁰⁹ thus the signals due to H-3 and H-4 form a simple AX spin-spin ($J = 6$ Hz) system without further coupling with the resonance of H-1.

Clearly the ring closure has occurred to give initially 3,4-dihydro-5,11-dimethyl-9-phenylsulphonyloxy-6*H*-pyrido[4,3-*b*]fluorene (137) which was then aromatised to our protected target (133) (scheme 38). The yield from the starting amide (132) was estimated to be 22 %. However, the ¹H n.m.r. spectrum indicates that

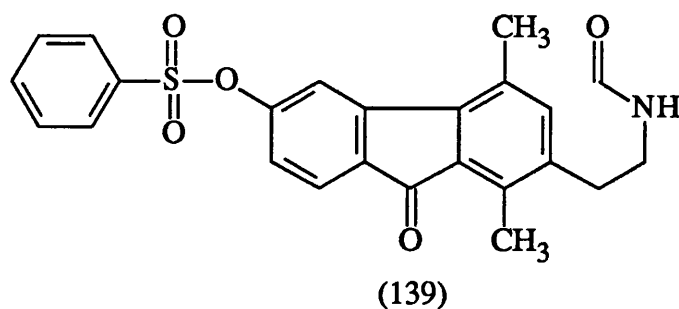
another product has also formed. Thus two extra methyl proton resonances appear as singlets at δ 2.75 and δ 2.95 [the corresponding signals for (133) occur at δ 2.59 and δ 2.77]. Interestingly the methine resonances of ring-D are now shifted upfield relative to positions occupied by the corresponding signals of the first product. The characteristic double doublet of the proton at C-8 is also shifted upfield from δ 6.98 to δ 6.88 and there is now no methylene signal due to protons at C-6.

The mass spectrum of the crude reaction product shows two molecular ions one at m/z 401 due to the fluorene (133) and the second at m/z 415. These results are consistent with the presence of 5,11-dimethyl-6-oxo-9-phenylsulphonyloxypyrido-[4,3-*b*]fluorene (138), comprising approximately 30 % of the product, arising from oxidation of the 6-methylene group.



A major effort was made to separate these two products but this failed and we were unable to isolate the compounds free from one another.

This result is not unprecedented as Dixit, Khanna and Anand ³⁹ obtained a mixture of 5,11-dimethyl-6*H*-pyrido[4,3-*b*]fluorene (24) and 5,11-dimethyl-6-oxopyrido[4,3-*b*]fluorene (25) in their final product from the cyclisation of 2-(2-formamidoethyl)-1,4-dimethylfluorene (30). The fact that the 6-methylene group is susceptible to oxidation may account, in part, for the low yield of our reaction. If the starting 2-(2-formamidoethyl)-1,4-dimethyl-6-phenylsulphonyloxyfluorene (132) is oxidised to 2-(2-formamidoethyl)-1,4-dimethyl-9-fluorenone (139) before cyclisation can occur, then the subsequent deactivation of the C-ring would make cyclisation highly unlikely.



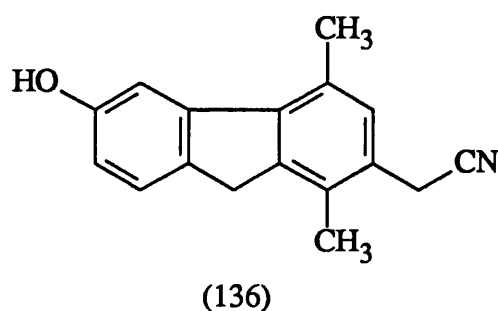
It should be noted that in each of Dixit's syntheses the yields were in the region of 30 %. The cyclisation also has to occur at the 3-position of the fluorene (132), which is less favoured and is also producing a hexasubstituted benzene ring which will have a large steric requirement.

We were pleased to have demonstrated the synthesis of the protected form of our target compound. The production of the 6-oxo product was unfortunate, however, Dixit, Khanna and Anand were able to take their crude mixture and obtain pure 5,11-dimethyl-6*H*-pyrido[4,3-*b*]fluorene (21) by Wolff - Kishner reduction.³⁹ Unfortunately by this time we had insufficient material to attempt the reduction and deprotection (which could be performed in one pot) and we were unable to complete the synthesis due to pressures of time.

This synthetic sequence leads to the protected target compound in 15 steps. The reduction of the nitrile (130) to the amine (131) gave a poor yield and the final cyclisation was disappointing but understandable. If repeated on a large enough scale this route will undoubtedly produce sufficient product for biological evaluation. One possible way of improving this route may lie in a strategic deprotection in mid sequence. The benzenesulphonyl protecting group offers two advantages, firstly it blocks the A-ring towards substitution and secondly it can withstand the harsh reaction conditions of the chloromethylation. Unfortunately the presence of this group inhibits the final cyclisation step.

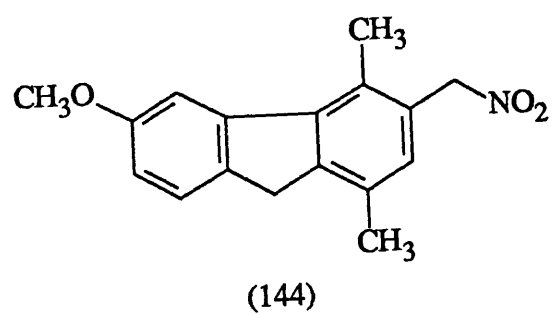
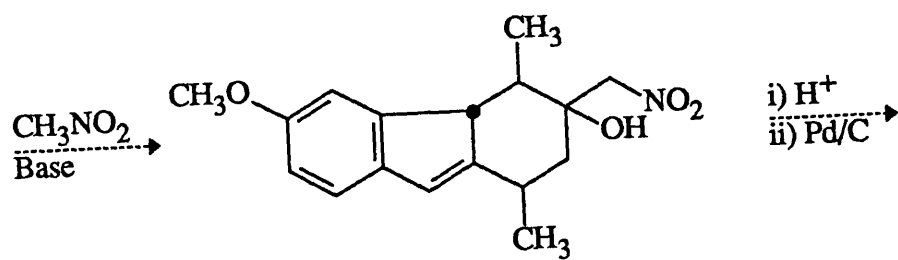
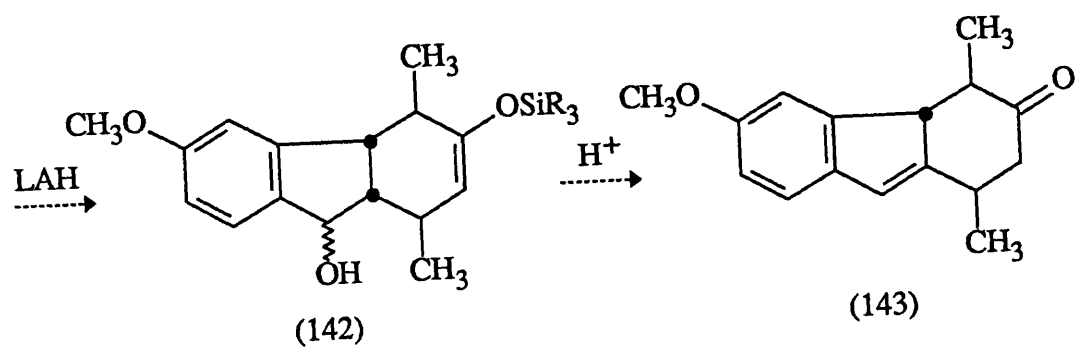
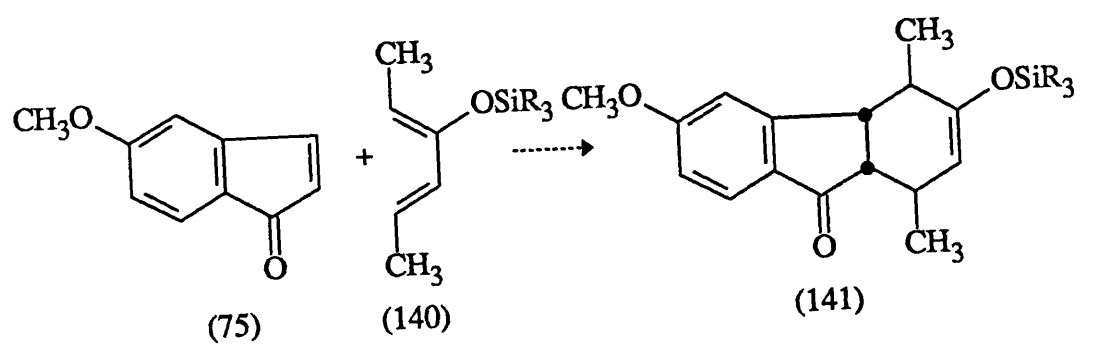
Probably the most appropriate point for release of the *O*-protection would be after the nitrile displacement reaction. However, since the benzenesulphonyl group is

normally removed by alkaline hydrolysis there is the possibility of competing hydrolysis of the nitrile group. One way round this problem may be to perform the cyanide displacement using two equivalents of sodium cyanide at an elevated temperature to produce 2-cyanomethyl-1,4-dimethyl-6-hydroxyfluorene (136). This could then be carried through the existing steps, possibly without reprotection of the phenol.



As already discussed the reaction sequence we investigated is unsatisfactory in the formation of ring-D. The preference for electrophilic attack at C-2 of ring-C of the fluorene (127) has been discussed, while it is helpful in the preparation of a single regio- isomer it does lead to the difficult ring closure onto C-3. The alternative would be to synthesise a suitable 3-substituted fluorene (as was explored in the 3-t-butyl-dimethylsilyloxymethyl-2,5-dimethylfuran Diels - Alder approach). One possible route, based on our chemistry, is as outlined in scheme 39.

Thus a Diels - Alder reaction between 5-methoxy-1-indenone and 3-silyloxy-2,4-hexadiene (140) (which should be prepared from hex-4-en-3-one) would give the adduct (141). Reduction should lead to the alcohols (142) elimination of which, with simultaneous deprotection, would give the ketone (143). Condensation with a suitable nucleophile (the nitromethane anion is shown) followed by aromatisation, would produce the desired 1,3,4,6-tetrasubstitutedfluorene (144) which should more readily be elaborated to the target product, with a much easier final ring closure. Unfortunately there was insufficient time available to explore these possibilities.



Scheme 39.

3. EXPERIMENTAL

All melting points were recorded using an Electrothermal Mk II melting point apparatus and were uncorrected.

Elemental analysis was carried out on a Carlo Erba 1106 Elemental Analyser.

Infrared spectra were determined as thin film, Nujol mull or chloroform solution (as stated) on a Perkin - Elmer 1310 Infrared spectrophotometer. All spectra were run over the range 4000 - 600 cm^{-1} .

Ultraviolet spectra were recorded on a Perkin-Elmer Lambda 3 UV / VIS Spectrometer and R 100 recorder, as solutions in 95 % ethanol, over the range 390 - 195 nm.

The ^1H n.m.r. spectra were recorded at 60 MHz on either a Hitachi Perkin-Elmer R - 24 B high resolution n.m.r. spectrometer or on a Varian EM 360. Spectra recorded at 100 MHz were recorded on a Jeol P.S. 100 spectrometer and at 270 MHz on a Jeol GMNGXFT - 270 spectrometer.

The ^{13}C n.m.r. spectra were recorded either at 22.5 MHz on a Jeol FX 92 spectrometer or at 67.8 MHz on a Jeol GMNGXFT - 270 spectrometer.

All n.m.r. spectra were recorded using tetramethylsilane (δ 0.00, s) as an internal standard and the multiplicities quoted in the spectral data are explained thus; (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet.

Mass spectrometry was carried out on a VG Analytical 7070 E instrument with a VG 200 data system. All compounds were investigated under electron impact (70 eV) for a molecular ion peak (M^+) or under isobutane chemical ionisation for a molecular ion peak + 1 ($M+1$).

Photochemical experiments were performed using Applied Photophysics apparatus.

Column chromatography using silica was performed using either the dry flash technique or medium pressure on Merck Kieselgel 60_H no 7736. Thin layer chromatography used Kieselgel 60 F₂₅₄ coated aluminium plates.

Chromatography on alumina was performed using Camag 100 - 250 mesh alumina under gravity. All alumina was Brockman grade I. Elution solvents used were as stated, petroleum ether refers to the boiling fraction 60 - 80 °C unless otherwise stated. All solvents and reagents were purified using standard techniques. ¹¹⁰

4-Bromo-2,5-dimethyl-(3-chloropropiono)phenone (54).

A mixture of 2-bromo-1,4-dimethylbenzene (20.32 g, 0.11 mol) and 3-chloropropionoyl chloride (14.58 g, 0.12 mol) in dry dichloromethane (30 cm³) was added dropwise to a suspension of aluminium chloride (18.34 g, 0.14 mol) in dry dichloromethane (80 cm³) over 20 minutes. After stirring for 2 h at room temperature, the reaction mixture was poured onto ice (400 cm³) and extracted with dichloromethane. The combined extracts were washed with saturated aqueous sodium bicarbonate, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to give a yellow solid. Trituration with methanol afforded the title compound as a colourless solid (23.5 g, 78 %), m.p. 91 - 92 °C (lit., ⁴⁰ 81 °C.); λ_{max} (EtOH) 210, and 250 nm; ν_{max} (CHCl₃) 1680 cm⁻¹ (C=O); δ_{H} (60 MHz, CDCl₃) 2.40 (6 H, s, Ar-CH₃), 3.30 (2 H, t, *J* = 6 Hz, 2'-CH₂), 3.83 (2 H, t, *J* = 6 Hz, 3'-CH₂), 7.40 (1 H, s, Ar-H), and 7.46 (1 H, s, Ar-H).

5-Bromo-4,7-dimethylindanone (55).

4-Bromo-2,5-dimethyl-(3-chloropropiono)phenone (19.85 g, 0.07 mol) was added, in portions over five minutes, to stirred concentrated sulphuric acid (150 cm³). The mixture was heated at 80 - 90 °C for 1 h, cooled, poured onto crushed ice (850 cm³), and extracted with dichloromethane. The combined extracts were washed with saturated aqueous sodium bicarbonate, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to give a pale yellow solid. Recrystallisation from ethanol afforded the title compound as colourless needles (12.8 g, 77 %), m.p. 106.5 - 107.5 °C (lit., ¹¹¹ 105 - 106 °C); λ_{max} (EtOH) 215, 262, and 295 nm; ν_{max} (CHCl₃) 1675 cm⁻¹ (C=O); δ_{H} (60 MHz, CDCl₃) 2.38 (3 H, s, Ar-CH₃), 2.56 (3 H, s, Ar-CH₃), 2.60 - 3.10 (4 H, m, -CH₂CH₂-), and 7.35 (1 H, s, 6-H).

5-Bromo-4,7-dimethylindanol (56).

Sodium borohydride (2.82 g, 0.075 mol) was added to a stirred ice - cooled suspension of 5-bromo-4,7-dimethylindanone (7.47 g, 0.03 mol) in methanol (175 cm³) at such a rate so as to maintain the solution temperature below 5 °C. When the addition was complete the stirred solution was allowed to warm to room temperature over 3 h before it was poured onto water (250 cm³) and extracted with dichloromethane. The combined extracts were washed with saturated aqueous sodium bicarbonate, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to afford a colourless solid (7.45 g, 99 %), which was used without purification. m.p. 122.5 - 126.5 °C (lit., ¹¹¹ 122 - 125 °C); λ_{max} (EtOH) 210 nm; ν_{max} (NUJOL) 3200 cm⁻¹ (-OH); δ_{H} (60 MHz, CDCl₃) 1.66 (1 H, s, exch. D₂O, -OH), 2.22 (3 H, s, Ar-CH₃), 2.30 (3 H, s, Ar-CH₃), 2.7 - 3.15 (4 H, m, -CH₂CH₂-), 5.16 (1 H, m, -CHOH), and 7.10 (1 H, s, 6-H).

6-Bromo-4,7-dimethylindene (57).

5 M Sulphuric acid (65 cm³) was added to a solution of 5-bromo-4,7-dimethylindanol (5.07 g, 0.02 mol) in tetrahydrofuran (250 cm³) and the mixture heated on an oil bath at 80 - 90 °C for 2 h. The cooled mixture was poured onto ice / water (250 cm³) and extracted with hexane. The combined extracts were dried (MgSO₄) and evaporated under reduced pressure to a pale yellow solid. Chromatography over florisil eluting with hexane afforded the title compound as a colourless solid (4.45 g, 95 %) m.p. 55 - 57 °C (lit., ¹¹¹ 53 - 54 °C); λ_{max} (EtOH) 216, 220, 228, 260, 288, and 302 nm; ν_{max} (CHCl₃) 1600, and 1580 cm⁻¹ (ArC-C); δ_{H} (60 MHz, CDCl₃) 2.36 (6 H, s, Ar-CH₃), 3.30 (2 H, m, Ar-CH₃), 6.50 (1 H, dt, J = 6 Hz and 2 Hz, 2-H), 6.90 (1 H, dt, J = 6 Hz and 2 Hz, 3-H), and 7.30 (1 H, s, 5-H).

6-Bromo-5,8-dimethylisoquinoline (47).

A solution of 6-bromo-4,7-dimethylindone (5.0 g, 0.02 mol) in dry dichloromethane (40 cm³) and dry methanol (80 cm³) was cooled to -78 °C under an atmosphere of dry nitrogen. Ozone was then bubbled through the reaction mixture until a blue colour persisted. Excess ozone was removed by degassing with nitrogen and the flask removed from the cooling bath. Dimethyl sulphide (5.4 cm³) and sodium bicarbonate (2.5 g) were added and the mixture shaken and allowed to stand at room temperature for 7 h. 2 M Ammonium hydroxide solution (30 cm³) was added and the mixture swirled and left to stand overnight. Work - up, for bases gave a pale yellow solid. Chromatography on silica gel eluting with ethyl acetate afforded the title compound as a colourless solid (3.1 g, 65 %) m.p. 106 - 110 °C (lit., ⁴⁰ 90 °C); λ_{max} (EtOH) 236, 280, 312 and 328 nm; ν_{max} (CHCl₃) 1600, and 1580 cm⁻¹ (Ar C-C); δ_{H} (60 MHz, CDCl₃) 2.60 (6 H, s, Ar-CH₃), 7.26 (1 H, s, 7-H), 7.50 (1 H, d, $J = 6$ Hz, 4-H), 8.35 (1 H, d, $J = 6$ Hz, 3-H), and 9.10 (1 H, brs, 1-H); m/z 235 (M^+) and 237(M^+).

4-Phenyloxyphenethyl alcohol (60).

Potassium hydroxide (3.14 g, 56 mmol) was added to a solution of 4-hydroxyphenethyl alcohol (6.5 g, 47 mmol) in dry methanol (100 cm³) and the mixture stirred until the base had dissolved. Benzyl chloride (7 g, 55 mmol) was added and the mixture heated under reflux for 3.25 h. The cooled mixture was poured onto water and extracted with ethyl acetate. The combined extracts were washed with 1 % aqueous potassium hydroxide solution, water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to give a pale cream solid. Recrystallisation from petroleum ether afforded the title compound as colourless needles (6.4 g, 60 %). m.p. 84 - 85 °C (lit., ⁴⁶ 83 - 85 °C); λ_{max} (EtOH) 224, 276 and 283 nm; ν_{max} (CHCl₃) 3420 (-OH), 1605, and 1580 cm⁻¹ (ArC-C); δ_{H} (100 MHz, d₆-DMSO) 2.68 (2 H, t, $J = 8$ Hz, Ar-CH₂CH₂), 3.55 (2 H, dt, $J = 6$ Hz and 8 Hz, CH₂CH₂OH), 4.60 (1 H, t, $J = 6$ Hz,

exch. D₂O, CH₂OH), 5.02 (2 H, s, Ar-CH₂O), 6.90 (2 H, d, J = 8 Hz, Ar-H), 7.10 (2 H, d, J = 8 Hz, Ar-H), 7.35 (5 H, m, Ar-H); m/z 228 (M^+ , 13 %), 91(100).

4-Phenyloxyphenylacetaldehyde (58).

A solution of 4-phenyloxyphenethyl alcohol (5 g, 22 mmol) in dry dichloromethane (35 cm³) was added to a stirred suspension of pyridinium chlorochromate (7.11 g, 33 mmol) in dry dichloromethane (35 cm³) and the mixture stirred for 1.5 h. Ether (250 cm³) was added to the reaction mixture and the solvent decanted. The black residue was washed with dry ether (3 x 50 cm³) and the combined solvents filtered through a short pad of florisil. The filtrate was concentrated *in vacuo* to 100 cm³ and stirred with saturated aqueous sodium metabisulphite solution (200 cm³) for 4.25 h. The resulting precipitate was filtered, washed with ether and stirred with saturated aqueous sodium carbonate (200 cm³) and ether (200 cm³) for 2.75 h. The ether was separated and washed with water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a pale cream solid (1.6 g, 32 %); ν_{\max} (NUJOL) 1720 (C=O), 1600, and 1580 cm⁻¹ (ArC-C); δ_{H} (60 MHz, CDCl₃) 3.50 (2 H, d, J = 3 Hz, -CH₂CHO), 5.0 (2 H, s, Ar-CH₂O), 7.10 (4 H, m, Ar-H), 7.45 (5 H, s, Ar-H), and 9.85 (1 H, t, J = 3 Hz, -CHO). This compound was unstable and was used immediately.

4-Methoxyphenylacetyl chloride (49, R = CH₃, X = Cl).

A mixture of 4-methoxyphenylacetic acid (5 g, 0.03 mol) and freshly distilled thionyl chloride (4.5 g, 0.038 mol) in dry toluene (50 cm³) was heated under reflux for 1.5 h. The solvent was removed *in vacuo* and bulb to bulb distillation of the residue afforded the title compound as a pink oil (5.4 g, 97 %), b.p._{0.4} 110 °C (lit. ¹¹² b.p.₁₀ 143 °C); ν_{\max} (Thin Film) 1800 (C=O), 1610, and 1580 cm⁻¹ (ArC-C); δ_{H} (60 MHz, CDCl₃) 3.76 (2 H, s, -CH₂COCl), 4.03 (3 H, s, Ar-OCH₃), 6.90 (2 H, d, J = 9 Hz, 3- and 5-H), and 7.20 (2 H, d, J = 9 Hz, 2- and 6-H).

Ethyl 4-methoxyphenyl acetate (49, R = CH₃, X = OC₂H₅).

A mixture of 4-methoxyphenylacetic acid (4.09 g, 25 mmol) and concentrated sulphuric acid (0.7 g) in absolute ethanol (14 g) was heated under reflux for 6 h. The cooled mixture was poured onto ice / water (25 cm³) and extracted with dichloromethane. The combined extracts were washed with saturated aqueous sodium bicarbonate, water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a pale yellow oil (4.4 g, 92 %). λ_{max} (EtOH) 226, 275 and 282 nm; ν_{max} (Neat) 1735 (C=O), 1605, and 1580 cm⁻¹ (ArC-C); δ_{H} (60 MHz, CDCl₃) 1.2 (3 H, t, J = 8 Hz, -OCH₂CH₃), 3.50 (2 H, s, -CH₂CO), 3.72 (3 H, s, -OCH₃), 4.05 (2 H, q, J = 8 Hz, -OCH₂CH₃), 6.80 (2 H, d, J = 9 Hz, 3- and 5-H), and 7.15 (2 H, d, J = 9 Hz, 2- and 6-H). This compound was not further characterised but used directly in the following reaction.

Anion reactions of 6-bromo-1,4-dimethylisoquinoline (48).

A solution of n-butyllithium (1.45 M in hexane) (1.5 cm³, 2.2 mmol) was added dropwise during 10 minutes to a solution of 6-bromo-5,8-dimethylisoquinoline (0.52 g, 2.2 mmol) in dry tetrahydrofuran (13 cm³) at -78 °C under an atmosphere of dry nitrogen and the mixture stirred for 0.75 h. A solution of the substrate (2.2 mmol) in dry tetrahydrofuran (10 cm³) was added dropwise during 20 minutes and the mixture allowed to warm to room temperature during 2.5 h. The mixture was poured onto saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with 2 M hydrochloric acid, water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure.

The acid washings were neutralised with saturated aqueous sodium carbonate and extracted with ethyl acetate. The combined extracts were washed with water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure.

Both products were examined by ^1H n.m.r. and thin layer chromatography.

With 4-phenyloxyphenylacetaldehyde, 4-methoxyphenylacetyl chloride and phenylacetaldehyde both extracts showed complex mixtures by thin layer chromatography, neither extract exhibited all the required peaks in the ^1H n.m.r. spectrum. With ethyl 4-methoxyphenyl acetate the non - basic extract yielded an oil which was predominantly recovered starting material. The basic extract yielded a complex gum.

In each of the basic extracts, although thin layer chromatography showed a number of components, one major product was observed: δ_{H} (60 MHz, CDCl_3) 2.55 (3 H, s), 2.68 (3 H, s), 7.20 (2 H, m), 7.6 (1 H, d, $J = 6$ Hz), 8.45 (1 H, brs), and 9.25 (1 H, brs). This data is consistent with 5,8-dimethylisoquinoline.

6-Deutero-5,8-dimethylisoquinoline (62).

A solution of n-butyllithium (1.6 M in hexane) (0.45 cm^3 , 0.7 mmol) was added dropwise, during 10 minutes, to a solution of 6-bromo-5,8-dimethylisoquinoline (150 mg, 0.64 mmol) in dry tetrahydrofuran (5 cm^3) at -78°C under an atmosphere of dry nitrogen and the mixture stirred for 0.75 h. Tetrahydrofuran (3 cm^3) containing deuterium oxide (0.5 cm^3) was added and the mixture warmed to room temperature during 2.5 h. The mixture was poured onto water and extracted with dichloromethane. The combined extracts were washed with saturated brine, dried (MgSO_4) and evaporated under reduced pressure to a red oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1:1) afforded the title compound as an orange oil (62 mg, 61 %). (Accurate mass found: 158.0936. $\text{C}_{11}\text{H}_{10}\text{ND}$ requires 158.0954.); δ_{H} (60 MHz, CDCl_3) 2.50 (3 H, s, Ar- CH_3), 2.65 (3 H, s, Ar- CH_3), 7.12 (1 H, s, 7-H), 7.6 (1 H, d, $J = 6$ Hz, 4-H), 8.45 (1 H, d, $J = 6$ Hz, 3-H), and 9.30 (1 H, brs, 1-H); m/z 158 (M^+ , 100 %), 143 (64).

2,5-Dimethylbenzyl chloride (67).

A mixture of distilled 1,4-xylene (50 g, 0.47 mol), glacial acetic acid (145 cm³), concentrated hydrochloric acid (315 cm³) and 37 % aqueous formaldehyde solution (33 g, 0.4 mol) was stirred at 50 - 60 °C for 24 h. Additional 37 % aqueous formaldehyde solution (9.5 g, 0.1 mol) was added and stirring continued for a further 24 h. The cooled mixture was extracted with benzene and the combined extracts washed with 10 % aqueous sodium carbonate, water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to a pale yellow oil. Distillation afforded the title compound as a colourless oil (49.9 g, 69 %) b.p._{0.3} 60 - 65 °C (Lit. ⁵⁰ b.p.₂ 104 - 106 °C) δ_{H} (60 MHz, CDCl₃) 2.20 (3 H, s, Ar-CH₃), 2.25 (3 H, s, Ar-CH₃), 4.35 (2 H, s, Ar-CH₂Cl), and 6.82 (3 H, s, Ar-H).

2,5-Dimethylbenzyltriphenylphosphonium chloride.

A mixture of 2,5-dimethylbenzyl chloride (20 g, 0.13 mol) and triphenylphosphine (34 g, 0.13 mol) in xylene (200 cm³) was heated under reflux for 20 h. The hot mixture was filtered to yield the title compound as a colourless solid (46.9 g, 67 %) m.p. 301 - 4 °C (lit., ⁵¹ 289 °C) (Found : C, 77.7; H, 6.4. C₂₇H₂₆ClP requires C, 77.8; H, 6.3 %); ν_{max} (CHCl₃) 1600 (ArC-C), and 1430 cm⁻¹ (P-Ph); δ_{H} (60 MHz, CDCl₃) 1.6 (3 H, s, Ar-CH₃), 2.0 (3 H, s, Ar-CH₃), 5.1 (2 H, d, J = 14 Hz, Ar-CH₂P), 6.66 (1 H, s, 6-H), 6.8 (2 H, s, 3- and 4-H), 7.5 (6 H, s, *o*-protons P⁺(Ph)₃), and 7.60 (9 H, s, *m*- and *p*-protons P⁺(Ph)₃); m/z (CI) 380 (M^+ -1, 38 %), and 263 (100).

This compound is described in a patent, ⁵¹ but no physical data were quoted for it.

4'-Methoxy-2,5-dimethylstilbene (65).

A 1.47 M solution of n-butyllithium in hexane (39.3 cm³, 0.058 mol) was added dropwise, during 0.25 h, to a suspension of 2,5-dimethylbenzyltriphenylphosphonium chloride (20 g, 0.048 mol) in dry benzene (150 cm³) under an atmosphere of dry nitrogen and the mixture stirred for 1.5 h. A solution of freshly distilled 4-anisaldehyde (7.84 g, 0.058 mol) in dry benzene (35 cm³) was added dropwise, during 0.25 h, and the mixture stirred overnight. Water (120 cm³) was added and the benzene layer separated. The water was extracted with benzene and the combined extracts washed with saturated brine and evaporated under reduced pressure. The residue was triturated with petroleum ether and the precipitated triphenylphosphine oxide filtered off. The filtrate was dried (Na₂SO₄) and evaporated under reduced pressure to give a pale yellow solid. Recrystallisation from aqueous ethanol afforded the title compound as colourless needles (8.0 g, 70 %), m.p. 76 - 78 °C (lit., 48 73 - 75 °C) (Found: C, 85.0; H, 7.8. Calc. for C₁₇H₁₈O: C, 85.7; H, 7.6 %); λ_{max} (EtOH) 207, 228 (sh), and 295 nm; ν_{max} (CHCl₃) 1600, and 960 cm⁻¹ (C=C); δ_{H} (270 MHz, CDCl₃) 2.33 (3 H, s, Ar-CH₃), 2.36 (3 H, s, Ar-CH₃), 3.78 (3 H, s, -OCH₃), 6.88 (2 H, d, J = 9 Hz, 3'- and 5'-H), 6.92 (1 H, d, J = 16 Hz, β -H), 6.96 (1 H, dd, J = 8 and 2 Hz, 4-H), 7.04 (1 H, d, J = 8 Hz, 3-H), 7.16 (1 H, d, J = 16 Hz, α -H), 7.38 (1 H, brs, 6-H), and 7.44 (2 H, d, J = 9 Hz, 2'- and 6'-H); m/z 238 (M^+ , 100 %).

6-Methoxy-1,4-dimethylphenanthrene(66).

A mixture of 4'-methoxy-2,5-dimethylstilbene (500 mg, 2.1 mmol) and iodine (100 mg, 0.4 mmol) in methanol (1.2 L) was irradiated with a 400 W. medium pressure lamp for 1 h. During the irradiation the solution was agitated by the passage of dry air. The methanol was evaporated under reduced pressure and the residue combined with that of a second identical run.

The combined residues were dissolved in chloroform and washed with 0.75 M sodium thiosulphate solution, water, saturated brine, dried (MgSO₄) and evaporated

under reduced pressure to a pale yellow solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 9) afforded the title compound as a colourless solid. (750 mg, 76 %), m.p. 70 °C (lit., ⁴⁸ 82 - 83 °C) (Found: C, 86.4; H, 6.8. Calc. for C₁₇H₁₆O: C, 86.4; H, 6.8 %) λ_{max} (EtOH) 202, 228, 255, 297, 308 and 360 nm; ν_{max} (CHCl₃) 1605, and 1585 cm⁻¹ (ArC-C); δ_{H} (270 MHz, CDCl₃) 2.66 (3 H, s, Ar-CH₃), 3.06 (3 H, s, Ar-CH₃), 3.91 (3 H, s, -OCH₃), 7.20 (1 H, dd, $J = 8.8$ Hz and 2 Hz, 7-H), 7.29 (2 H, s, 9- and 10-H), 7.63 (1 H, d, $J = 9$ Hz, 2-H), 7.77 (1 H, d, $J = 8.8$ Hz, 8-H), 7.78 (1 H, d, $J = 9$ Hz, 3-H), and 8.28 (1 H, d, $J = 2$ Hz, 5-H); m/z 236 (M^+ , 100 %), 221 (25), and 151 (57).

Attempted Vilsmeier formylation of 6-methoxy-1,4-dimethylphenanthrene.

Freshly distilled phosphorus oxychloride (100 mg, 0.7 mmol) was added dropwise to dry *N,N*-dimethylformamide (3.2 cm³) at 0 °C and the mixture stirred for 15 minutes. A solution of 6-methoxy-1,4-dimethylphenanthrene (150 mg, 0.6 mmol) in dry *N,N*-dimethylformamide (4 cm³) was added dropwise to the cold solution and the mixture allowed to warm to room temperature over 1 h. Thin layer chromatographic analysis revealed no change and the mixture was heated at 100 °C for 1 h. The cooled mixture was poured onto crushed ice, neutralised with saturated aqueous sodium acetate and extracted with chloroform. The combined extracts were washed with water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to a brown solid. ¹H n.m.r. showed this to be recovered 6-methoxy-1,4-dimethylphenanthrene.

9,10-Dihydro-6-methoxy-1,4-dimethylphenanthrene (68).

A solution of 6-methoxy-1,4-dimethylphenanthrene (150 mg, 0.6 mmol) in ethyl acetate (50 cm³) was shaken with 10 % palladium on carbon (45 mg) under an atmosphere of hydrogen at 40 p.s.i. for 50 h. The catalyst was removed by filtration through celite and the solvent evaporated to give an oil. Dry column flash

chromatography eluting with ethyl acetate - petroleum ether (1: 9) afforded the title compound as a pale yellow oil (130 mg, 86 %). λ_{max} (EtOH) 220, 261, 267, and 296 nm; δ_{H} (60 MHz, CDCl_3), 2.25 (3 H, s, Ar- CH_3), 2.55 (3 H, s, Ar- CH_3), 2.60 (4 H, s, 9- and 10- CH_2), 3.70 (3 H, s, $-\text{OCH}_3$), 6.6 (1 H, dd, $J = 8$ Hz and 2 Hz, 7-H), 6.85 (2 H, s, 2- and 3-H), 7.05 (1 H, d, $J = 8$ Hz, 8-H), and 7.02 (1 H, d, $J = 2$ Hz, 5-H); m/z 238 (M^+ , 100 %), and 223 (46).

Attempted preparation of 6-methoxy-1,4-dimethylphenanthrenequinone (71).

Concentrated sulphuric acid (0.8 cm^3) was added dropwise to a stirred mixture of 6-methoxy-1,4-dimethylphenanthrene (200 mg, 0.8 mmol) and chromium(VI) oxide (320 mg, 3.2 mmol) in water (5 cm^3). When the addition was complete a solution of chromium(VI) oxide (320 mg, 3.2 mmol) in water (3 cm^3) was added dropwise during 40 minutes and the mixture heated under reflux for 30 minutes. The cooled mixture was poured onto water, chilled in an ice bath and the crude product collected at the pump and washed with water until the washings were clear. The orange solid was triturated with boiling water (3 x 10 cm^3) and dried to give a dark yellow solid (130 mg). Thin layer chromatographic analysis showed this to be a complex mixture not containing any starting material.

Large scale photochemical reaction.

A mixture of 4'-methoxy-2,5-dimethylstilbene (3 g, 0.013 mol) and iodine (600 mg, 2.4 mmol) in methanol (9.5 L) was stirred rapidly and irradiated with four 400 W medium pressure lamps for 2.25 h. The methanol was evaporated under reduced pressure and the residue taken up in chloroform. The chloroform was washed with 0.75 M sodium thiosulphate solution, water, saturated brine, dried (MgSO_4) and evaporated under reduced pressure to a yellow solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 9) afforded a colourless solid (1.75 g).

^1H n.m.r. δ_{H} (60 MHz, CDCl_3) showed this to be a 1:1 mixture of 4'-methoxy-2,5-dimethylstilbene and 6-methoxy-1,4-dimethylphenanthrene.

Ethyl 2,5-dimethylfuran-3-carboxylate (76, $\text{R} = \text{CO}_2\text{C}_2\text{H}_5$).

Dry ethanol (100 cm^3) was added rapidly, with cooling, to sodium metal (17.2 g, 0.75 mol). When the initial reaction had subsided additional dry ethanol (400 cm^3) was added at such a rate so as to maintain gentle reflux. When the addition was complete ethyl acetoacetate (97.6 g, 0.75 mol) was added dropwise and the mixture stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the resulting solid dissolved in dry acetone (300 cm^3), sodium iodide (1.5 g, 0.01 mol) was added and the mixture heated under reflux. Chloroacetone (72 g, 0.78 mol) was added, during 30 minutes, and the mixture heated for a further hour.

The solvent was removed *in vacuo*, the residue added to water and extracted with ether. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to a red oil. Distillation under reduced pressure afforded two fractions; b.p.₁₃ 70 - 80 °C, a mixture of ethyl acetoacetate and chloroacetone (12.36 g), and the main fraction, ethyl α -acetylacrylate (93.9 g, 67 %) b.p.₁₃ 115 - 120 °C (lit., ⁶⁶ b.p.₁₂ 100 - 105 °C); ν_{max} (Neat) 1740 (sh), and 1710 cm^{-1} ($\text{C}=\text{O}$); δ_{H} (60 MHz, CDCl_3) 1.25 (3 H, t, $J = 6\text{ Hz}$, $-\text{OCH}_2\text{CH}_3$), 2.12 (3 H, s, 5- CH_3), 2.26 (3 H, s, COCH_3), 2.90 (1 H, d, $J = 2\text{ Hz}$, 3-H), 3.0 (1 H, d, $J = 2\text{ Hz}$, 3-H), and 4.0 (3 H, m, 2-H and $\text{CH}_3\text{CH}_2\text{O}-$).

Upon standing for two weeks this product turned dark red, redistillation afforded the title compound as a colourless oil (67.7 g, 54 %) b.p.₁₃ 90 - 95 °C (lit., ⁶⁶ b.p.₂₆ 110 - 111 °C); λ_{max} (EtOH) 200, and 253 nm; ν_{max} (Neat) 1700 ($\text{C}=\text{O}$), 1610, and 1580 cm^{-1} ; δ_{H} (60 MHz, CDCl_3) 1.30 (3 H, t, $J = 6\text{ Hz}$, $-\text{OCH}_2\text{CH}_3$), 2.18 (3 H, s, 5- CH_3), 2.45 (3 H, s, 2- CH_3), 4.15 (2 H, q, $J = 6\text{ Hz}$, $-\text{OCH}_2\text{CH}_3$), and 6.06 (1 H, s, 4-H); m/z 168 (M^+ , 59 %), 139 ($M^+ - \text{C}_2\text{H}_5$, 100), 123 ($M^+ - \text{OC}_2\text{H}_5$, 70), and 43 (72).

2,5-Dimethylfuran-3-methanol (84).

Ethyl 2,5-dimethylfuran-3-carboxylate (5.85 g, 0.035 mol) in dry ether (10 cm³) was added to a stirred suspension of lithium aluminium hydride (0.83 g, 0.022 mol) in dry ether (10 cm³), under dry nitrogen, at such a rate so as to maintain gentle reflux of the solvent. When the addition was complete the mixture was heated under reflux for 0.5 h. Wet ether (5 cm³) was added to the cooled mixture to destroy the excess hydride and the mixture was poured onto 38 % sodium potassium tartrate solution (30 cm³). The organic layer was separated and the aqueous extracted with ether. The combined extracts were washed with saturated brine, dried (MgSO₄) and evaporated under reduced pressure to a colourless oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title product as a colourless oil (4.2 g, 95 %); λ_{max} (EtOH) 218 nm; ν_{max} (Neat) 3350 (br, -OH), 1630, and 1580 cm⁻¹; δ_{H} (60 MHz, CDCl₃) 2.0 (1 H, s, exch. D₂O, -CH₂OH), 2.22 (6 H, s, 2- and 5-CH₃), 4.35 (2 H, s, -CH₂OH), and 5.90 (1 H, s, 4-H); m/z 126 (M^+ , 48 %), 108 (M -18, 31), and 43 (100). This compound darkened rapidly and was used immediately in the next step.

3-t-Butyldimethylsilyloxymethyl-2,5-dimethylfuran (85).

A mixture of 2,5-dimethylfuran-3-methanol (4 g, 0.032 mol), t-butyldimethylchlorosilane (5.31 g, 0.035 mol) and imidazole (4.79 g, 0.07 mol) in dry *N,N*-dimethylformamide (15 cm³) was stirred at room temperature for 16 h. The mixture was diluted with water and extracted with chloroform. The combined extracts were washed with water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to a yellow oil. Chromatography on silica eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a colourless oil (7.3 g, 95 %) b.p.₂₀ 150 °C (Found: C, 64.9; H, 10.4. C₁₃H₂₄O₂Si requires C, 64.95; H, 10.1 %); ν_{max} (CHBr₃) 1635, 1580 (C=C), 1070, and 835 cm⁻¹ (C-O-Si); δ_{H} (60 MHz, CDCl₃) 0.06 (6 H, s, -OSi(CH₃)₂), 0.9 (9 H, s, -OSiC(CH₃)₃), 2.18 (6 H, s, 2- and 5-CH₃),

4.4 (2 H, s, -CH₂O), and 5.82 (1 H, s, 4-H); *m/z* 240 (*M*⁺, 11 %), 225 (4), 183 (*M*-57, 100), 109 (*M*-131, 88), and 75 (95).

5-Methoxy-1-indanone (82).

3-(3-Methoxyphenyl)propionic acid (5 g, 0.028 mol) was added, in portions during 5 minutes, to polyphosphoric acid (28 g) at 50 °C and the mixture stirred at 50 °C for 3 h. The cooled mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with 0.5 M sodium hydroxide solution, water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to afford the title compound as a pale yellow solid. (3.8 g, 84 %) m.p. 108.5 - 109.5 °C (Petroleum ether) lit., ⁷⁰ 108 - 110 °C; (Found: C, 74.1; H, 6.2. Calc. for C₁₀H₁₀O: C, 74.1; H, 6.2 %; ν_{\max} (NUJOL) 1700 (C=O), 1600, and 1580 cm⁻¹ (ArC-C); δ_{H} (100 MHz, CDCl₃) 2.62 (2 H, t, *J* = 6 Hz, 2-CH₂), 3.05 (2 H, brt, *J* = 6 Hz, 3-CH₂), 3.83 (3 H, s, -OCH₃), 6.85 (2 H, m, 5- and 7-H), and 7.66 (1 H, d, *J* = 8 Hz, 8-H); δ_{C} (22.5 MHz, CDCl₃) 25.87, (t, 3-C), 36.43 (t, 2-C), 55.63 (q, -OCH₃), 109.71 (d, 4-C), 115.29 (d, 6-C), 125.30 (d, 7-C), 130.41 (s, 7a-C), 158.20 (s, 3a-C), 165.24 (s, 5-C), and 205.32 (s, 1-C); *m/z* 162 (*M*⁺, 100 %), and 134 (30).

3-Bromo-5-methoxy-1-indanone (83).

N-Bromosuccinimide (16 g, 0.09 mol) was added, in four portions during one hour, to a solution of 5-methoxy-1-indanone (12 g, 0.07 mol) and benzoylperoxide (100 mg, 0.4 mmol) in deoxygenated carbon tetrachloride (150 cm³). When the addition was complete the mixture was heated under reflux for 3 h, with spot lamp irradiation. The precipitated succinimide was filtered from the cooled mixture and the filtrate washed with water, saturated brine, dried (Na₂SO₄) and evaporated under

reduced pressure to an orange oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a yellow solid (15 g, 70 %). m.p. 70.5 - 71.5 °C (Found: C, 49.7; H, 3.9; Br, 32.95. $C_{10}H_9O_2Br$ requires: C, 49.8; H, 3.8; Br, 33.1 %); $\lambda_{\max}(\text{EtOH})$ 229 (ϵ 32 350 $\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$), and 274 nm (25 240); $\nu_{\max}(\text{CHCl}_3)$ 1710 (C=O), and 1600 cm^{-1} (ArC-C); $\delta_{\text{H}}(100 \text{ MHz}, \text{CDCl}_3)$ 3.0 (1 H, dd, $J = 16 \text{ Hz}$ and 4 Hz, 2 β -H), 3.40 (1 H, dd, $J = 16 \text{ Hz}$ and 8 Hz, 2 α -H), 3.92 (3 H, s, -OCH₃), 5.55 (1 H, dd, $J = 8 \text{ Hz}$ and 4 Hz, 3-H), 7.05 (1 H, dd, $J = 8 \text{ Hz}$ and 2 Hz, 6-H), 7.12 (1 H, d, $J = 2 \text{ Hz}$, 4-H), and 7.7 (1 H, d, $J = 8 \text{ Hz}$, 7-H); $\delta_{\text{C}}(22.5 \text{ MHz}, \text{CDCl}_3)$ 40.79 (d, 3-C), 48.26 (t, 2-C), 55.9 (q, -OCH₃), 110.29 (d) and 117.88 (d, 4- and 6-C, interchangeable), 124.98 (d, 7-C), 129.31 (s, 7a-C), 157.05 (s, 4a-C), 165.88 (s, 5-C), and 199.42 (s, 1-C); m/z 242 (M^+ , 9 %), 240 (M^+ , 9) and 161 (100, M -Br).

5-Methoxy-1-indenone (75).

Method A.

A mixture of 3-bromo-5-methoxy-1-indanone (4.5 g, 19 mmol) and 2,4,6-collidine (60 cm^3) in dry ether (50 cm^3) was stirred at room temperature for 2.5 h then at 50 °C for 3 h. The precipitated collidine hydrobromide was filtered from the cooled mixture and the filtrate acidified with ice cold hydrochloric acid - water (1:1). The collidine hydrochloride formed was filtered off and the organic layer of the filtrate separated, washed with water, saturated aqueous sodium carbonate, saturated aqueous copper sulphate, water, dried (MgSO_4) and evaporated under reduced pressure to an orange oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 9) afforded the title compound as a yellow oil (2.6 g, 84 %); (Accurate mass found: 160.0520. $C_{10}H_8O_2$ requires: 160.0522.); $\lambda_{\max}(\text{EtOH})$ 217, 258, and 333 nm; $\nu_{\max}(\text{CHCl}_3)$ 1700 (C=O), and 1600 cm^{-1} (ArC-C); $\delta_{\text{H}}(60 \text{ MHz}, \text{CDCl}_3)$ 3.80 (3 H, s, -OCH₃), 5.85 (1 H, d, $J = 6 \text{ Hz}$, 2-H), 6.52 (1 H, dd, $J = 8 \text{ Hz}$ and 2 Hz, 6-H), 6.6 (1 H, s, 4-H), 7.30 (1 H, d, $J = 8 \text{ Hz}$, 7-H), and 7.40 (1 H, d, $J = 6 \text{ Hz}$, 3-H);

m/z 160 (M^+ , 100 %), 89 (30), and 63 (30).

Attempted preparation of 4a,9a-dihydro-6-methoxy-1,4-dimethyl-1,4-epoxy-9-fluorenone-2- or 3- methanol.

A mixture of 5-methoxy-1-indenone (300 mg, 1.9 mmol) and 2,5-dimethyl-furan-3-methanol (230 mg, 1.8 mmol) in toluene (25 cm³) was heated at 80 °C for 14 h then under reflux for h. The toluene was evaporated under reduced pressure to give an orange oil. Thin layer chromatography showed this to be a complex mixture.

t-Butyldimethylsilyloxymethyl-4a,9a-dihydro-6-methoxy-1,4-dimethyl-1,4-epoxy-9-fluorenone (86).

A mixture of 5-methoxy-1-indenone (0.86 g, 5.37 mmol) and 2,5-dimethyl-3-t-butyldimethylsilyloxymethylfuran (1.28 g, 5.32 mmol) in chloroform was heated at 80 °C for 48 h. The chloroform was evaporated under reduced pressure to give a brown slurry. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4 - 1:1) gave three products; i) A colourless oil, recovered furan (370 mg, 30 %), ii) a yellow gum, recovered indenone (83 mg, 10 %), and iii) the title compound (506 mg, 33 %) a mixture of two isomers.

Preparative thin layer chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded one of the isomers as a colourless solid. m.p. 117 - 118.5 °C (Found: C, 69.2; H, 8.0 C₂₃H₃₂O₄Si requires: C, 68.9; H, 8.05 %); ν_{\max} (CHBr₃) 1695 (C=O), 1605, 1598, 1580 (ArC-C), 1250 (C-O-C), and 835 cm⁻¹(C-O-Si); δ_{H} (250 MHz, CDCl₃) 0.16 (6 H, s, -OSi(CH₃)₂), 0.78 (9 H, s, -OSiC(CH₃)₃), 1.75 (3 H, s, -CH₃), 1.77 (3 H, s, -CH₃), 3.18 (1 H, d, J = 8 Hz, 9a-H), 3.39 (1 H, dd, J = 16 Hz and 2 Hz, CH₂-OSi), 3.76 (1 H, d, J = 8 Hz, 4a-H), 3.82 (1 H, dd, J = 16 Hz and 2 Hz, CH₂OSi), 3.88 (3 H, s, -OCH₃), 5.84 (1 H, s, 2- or 3-H), 6.85 (1 H, s, 5-H), 6.88 (1 H, dd, J = 8 Hz and 2 Hz, 7-H), and 7.55 (1 H, d, J = 8 Hz, 8-H).

Attempted preparation of t-butyldimethylsilyloxymethyl-6-methoxy-1,4-dimethyl-9-fluorenone (89).

Method A.

A 1.8 M solution of n-butyllithium (0.65 cm³, 1.2 mmol) was added dropwise to a stirred solution of dry hexamethyldisilazane (0.25 cm³, 0.2 mmol) in dry tetrahydrofuran (10 cm³) under a dry nitrogen atmosphere at -78 °C and the mixture stirred for 0.5 h. A solution of t-butyldimethylsilyloxymethyl-4a,9a-dihydro-6-methoxy-1,4-dimethyl-1,4-epoxy-9-fluorenone (420 mg, 1.05 mmol) in dry tetrahydrofuran (5 cm³) was added, during 10 minutes, and the mixture warmed to 0 °C during 1.5 h. The mixture was quenched with saturated aqueous ammonium chloride (7 cm³), extracted with chloroform and the combined extracts dried (Na₂SO₄) and evaporated under reduced pressure to an orange oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded an orange oil (290 mg). ¹H n.m.r. showed this to be recovered starting material (70 % recovery).

Method B.

A solution of t-butyldimethylsilyloxymethyl-4a,9a-dihydro-6-methoxy-1,4-dimethyl-1,4-epoxy-9-fluorenone (170 mg, 0.4 mmol) in ethyl acetate (10 cm³) was stirred with 10 % palladium on carbon (50 mg) under hydrogen at atmospheric pressure for 15 minutes. The catalyst was removed by filtration through celite and the solvent evaporated under reduced pressure to a pale yellow gum. The gum was stirred with concentrated sulphuric acid (5 cm³) at 0 °C for 1 h, poured onto ice and extracted with dichloromethane. The combined extracts were washed with saturated aqueous sodium carbonate, water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to a red gum.

Thin layer chromatographic analysis of the gum revealed this to be a multi - component mixture. A repeat of this reaction but heating the reduced adduct with 1 M sulphuric acid under reflux for 1.5 h produced the same result.

Method C.

A mixture of *t*-butyldimethylsilyloxymethyl-4a,9a-dihydro-6-methoxy-1,4-dimethyl-1,4-epoxy-9-fluorenone (140 mg, 0.35 mmol) and *N*-bromosuccinimide (120 mg, 0.7 mmol) in carbon tetrachloride was heated under reflux for 4 h. The succinimide was filtered from the cooled mixture and the filtrate evaporated under reduced pressure to an orange gum. Thin layer chromatographic analysis revealed this to be a complex mixture.

3-(2'-Pentyl)-pyridine (99).

A 1.6 M solution of *n*-butyllithium in hexane (3 cm³, 4.67 mmol) was added dropwise to a stirred solution of dry diisopropylamine (0.65 cm³, 4.67 mmol) in dry tetrahydrofuran (5 cm³) under a dry nitrogen atmosphere at 0 °C. The reaction mixture was stirred for 0.5 h and hexamethylphosphoric triamide (0.81 cm³, 4.67 mmol) was added and the mixture stirred for a further 0.25 h. The mixture was cooled to -10 °C and a solution of dry 3-ethylpyridine (0.52 cm³, 4.67 mmol) in dry tetrahydrofuran (5 cm³) was added dropwise during five minutes. When the addition was complete the mixture was stirred for 0.5 h at -10 °C. A solution of 1-bromopropane (0.6 cm³, 6.6 mmol) in dry tetrahydrofuran (5 cm³) was added dropwise during five minutes and the mixture allowed to warm to room temperature during 1 h. The reaction mixture was poured onto 10 % hydrochloric acid (35 cm³) and the aqueous layer separated and basified with solid potassium hydroxide. The basic solution was extracted with ether and the combined extracts washed with water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to a yellow oil. Dry column flash chromatography eluting with methanol - ethyl acetate (1: 99) afforded the title compound as a pale yellow oil

(315 mg, 45 %). (Accurate mass found; 149.1203. C₁₀H₁₅N requires: 149.1203.); ν_{\max} (Neat) 1570 cm⁻¹; δ_{H} (60 MHz, CDCl₃) 0.85 (3 H, d, J = 6 Hz, 5'-CH₃), 1.25 (3 H, d, J = 8 Hz, 1'-CH₃), 1.3 - 1.7 (4 H, brm, 3'- and 4'- aliphatics), 2.60 (1 H, m,

$J = 8$ Hz, 2'-H), 7.0 (1 H, m, 5-H), 7.35 (1 H, m, 4-H), and 8.28 (2 H, brs, 2- and 6-H); δ_{C} (22.5 MHz, CDCl_3) 13.98 (q, 5'-C), 20.84 (t, 4'-C), 21.94 (q, 1'-C), 37.22 (d, 2'-C), 40.36 (t, 3'-C), 123.30 (d, 5-C), 134.08 (d, 4-C), 142.75 (s, 3-C), 147.41 (d, 6-C), and 149.20 (d, 2-C); m/z 149 (M^+ , 21 %), and 106 (100).

A second product was obtained; a pale yellow oil (220 mg). ^1H n.m.r. showed this to be recovered 3-ethylpyridine (44 % recovery).

Attempted preparation of 3-1'-(3'-pyridyl)ethyl-5-methoxy-1-indanone (95).

A 1.56 M solution of n-butyllithium in hexane (2.8 cm³, 4.37 mmol) was added dropwise to a stirred solution of dry diisopropylamine (0.65 cm³, 4.67 mmol) in dry tetrahydrofuran (4 cm³) under a dry nitrogen atmosphere at 0 °C. The reaction mixture was stirred for 0.5 h and hexamethylphosphoric triamide (0.75 cm³, 4.3 mmol) was added and the mixture stirred for a further 0.25 h. A solution of dry 3-ethylpyridine (0.5 cm³, 4.45 mmol) in dry tetrahydrofuran (4 cm³) was added dropwise during five minutes. When the addition was complete the mixture was stirred for 0.5 h at 0 °C. A solution of 3-bromo-5-methoxy-1-indanone (1 g, 4.15 mmol) in dry tetrahydrofuran (8 cm³) was added dropwise during five minutes and the mixture allowed to warm to room temperature during 1 h. The mixture was poured onto 10 % hydrochloric acid and the aqueous layer separated and basified with solid potassium hydroxide. The basic solution was extracted with ethyl acetate and the combined extracts washed with water, saturated brine, dried (Na_2SO_4) and evaporated to a black gum. Thin layer chromatographic analysis of this showed it to be a complex mixture.

Attempted preparation of 3-bromo-1,1,5-trimethoxyindan (100).

A mixture of 3-bromo-5-methoxy-1-indanone (500 mg, 2.07 mmol), trimethylorthoformate (300 mg, 2.8 mmol) and 4-toluenesulphonic acid (30 mg, 0.2 mmol) in dry methanol (6 cm³) was stirred at room temperature for 24 h. The black

mixture was neutralised with solid sodium carbonate and the solvent removed *in vacuo*. The residue was taken up in ether, washed with saturated aqueous sodium bicarbonate, water, dried (Na_2SO_4) and evaporated to a black gum. Thin layer chromatographic analysis and ^1H n.m.r. showed this to be a mixture containing predominantly 3-bromo-5-methoxy-1-indanone.

Attempted preparation of 1,1,5-trimethoxyindan (101).

A mixture of 5-methoxy-1-indanone (340 mg, 2.1 mmol), trimethylorthoformate (300 mg, 2.8 mmol) and 4-toluenesulphonic acid (30 mg, 0.2 mmol) in dry methanol (6 cm^3), was stirred at room temperature for 24 h. The solution was neutralised with solid sodium carbonate and concentrated *in vacuo*. The residue was dissolved in ether, washed with saturated aqueous sodium bicarbonate, water, dried (Na_2SO_4) and evaporated under reduced pressure to a yellow solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded a colourless solid (220 mg) m.p. 108 - 109.5 $^\circ\text{C}$, recovered 5-methoxy-1-indanone. This reaction was repeated, with the same result, using the following conditions; 1) heating under reflux for 5 h, 2) stirring at room temperature in the presence of activated 4 Å molecular sieves for 20 h., 3) heating under reflux in benzene in a Dean - Stark apparatus for 5 h.

Attempted preparation of 2-(5'-methoxy-1'-indanyl)-1,3-dioxolane (102).

A mixture of 5-methoxy-1-indanone (200 mg, 1.2 mmol) and 4-toluenesulphonic acid (20 mg, 0.1 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (5 cm^3 , 0.037 mol) was heated under reflux, under an atmosphere of dry nitrogen for 6 h. The cooled mixture was diluted with benzene - chloroform (1:1) and washed with 5 % aqueous sodium bicarbonate, saturated brine, dried (Na_2SO_4) and evaporated to a pale brown solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (2: 3) afforded a colourless solid (18 mg). ^1H n.m.r.(60 MHz, CDCl_3) showed

this to be recovered 5-methoxy-1-indanone.

Attempted preparation of 2-(5'-methoxy-1'-indanyl)-1,3-dioxane (104).

A mixture of 5-methoxy-1-indanone (200 mg, 1.23 mmol), propane-1,3-diol (100 mg, 1.35 mmol) and 4-toluenesulphonic acid (30 mg, 0.2 mmol) in dry benzene (30 cm³) was heated under reflux in a Dean - Stark apparatus for 24 h. The mixture was diluted with chloroform and washed with saturated aqueous sodium carbonate, water, dried (Na₂SO₄) and evaporated under reduced pressure to a pale yellow solid (180 mg) m.p. 102 - 104 °C. ¹H n.m.r. (60 MHz, CDCl₃) showed this to be recovered 5-methoxy-1-indanone.

Attempted preparation of 2-(3'-bromo-5'-methoxy-1'-indanyl)-1,3-dioxolane.

A mixture of 3-bromo-5-methoxy-1-indanone (5 g, 0.021 mol), 1,2-ethanediol (1.3 g, 0.021 mol) and 4-toluenesulphonic acid (50 mg, 0.26 mmol) in dry benzene (125 cm³) was heated under reflux in a Dean - Stark apparatus for 24 h. Additional 1,2-ethanediol was added and the mixture heated for a further 24 h. The cooled mixture was diluted with chloroform, washed with saturated aqueous sodium carbonate, water, dried (Na₂SO₄) and evaporated under reduced pressure to a black gum. Thin layer chromatographic analysis showed this to be predominantly unchanged 3-bromo-5-methoxy-1-indanone.

2-(5'-Methoxy-1'-indanyl)-1,3-dioxolane (102).

A mixture of 5-methoxy-1-indanone (3 g, 0.018 mol), 1,2-ethanediol (1.12 g, 0.018 mol) and 4-toluenesulphonic acid (30 mg, 1.6 mmol) in dry benzene (125 cm³) was heated under reflux in a Dean - Stark apparatus for 5 days. Additional 1,2-ethanediol (500 mg, 8 mmol) was added after 24 and 48 hours. The cooled mixture was filtered and the filtrate diluted with chloroform. The mixture was washed with saturated aqueous sodium carbonate, water, dried (Na₂SO₄) and evaporated under reduced

pressure to an orange oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 9 - 1: 4) afforded two products: i) a colourless solid m.p. 108 - 110 °C, recovered 5-methoxy-1-indanone (2.5 g, 83 % recovery), and ii) the title compound as a pale yellow oil (355 mg, 10 %); (Accurate mass found: 206.0943. $C_{12}H_{14}O_3$ requires: 206.0941.); ν_{\max} (NUJOL) 1600 (C=C), 1305, and 1260 cm^{-1} (C-O-C); δ_H (100 MHz, $CDCl_3$) 2.30 (2 H, t, $J = 7$ Hz, 2-CH₂), 2.90 (2 H, t, $J = 7$ Hz, 3-CH₂), 3.78 (3 H, s, -OCH₃), 4.10 (4 H, brm, -OCH₂CH₂O-), 6.70 (1 H, s, 4-H), 6.76 (1 H, dd, $J = 8$ Hz and 2 Hz, 6-H), and 7.22 (1 H, d, $J = 8$ Hz, 7-H); δ_C (22.5 MHz, $CDCl_3$) 28.50 (t, 3-C), 37.38 (t, 2-C), 55.37 (q, -OCH₃), 64.96 (t, -OCH₂CH₂O), 109.49 (d, 4-C), 113.66 (d, 6-C), 117.02 (s, 1-C), 124.01 (d, 7-C), 134.14 (s, 7a-C), 145.46 (s, 3a-C), and 161.17 (s, 5-C); m/z 206 (M^+ , 34 %), 176 (30), 162 (52), and 147 (100).

2-(5'-Methoxy-1'-indanyl)-1,3-dithiolane (108).

Boron trifluoride etherate (0.2 cm³, 1.6 mmol) was added slowly to a mixture of 5-methoxy-1-indanone (2 g, 0.012 mol) and 1,2-ethanedithiol (2 cm³, 0.024 mol) in dry dichloromethane (20 cm³) under an atmosphere of dry nitrogen, at 0 °C. The mixture was stirred at room temperature for 48 h, diluted with dichloromethane and washed with 5 % aqueous sodium hydroxide, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to an orange oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a colourless solid (2.55 g, 89 %) m.p. 57 °C (Accurate mass found: 238.0477. $C_{12}H_{14}OS_2$ requires: 238.0485.); ν_{\max} ($CHCl_3$) 1608, and 1585 cm^{-1} (ArC-C); δ_H (100 MHz, $CDCl_3$) 2.68 (2 H, t, $J = 6$ Hz, 2-CH₂), 2.98 (2 H, brt, $J = 6$ Hz, 3-CH₂), 3.44 (2 H, d, -SCH₂-), 3.46 (2 H, d, -SCH₂-), 3.78 (3 H, s, -OCH₃), 6.72 (1 H, s, 4'-H), 6.80 (1 H, dd, $J = 8$ Hz and 2 Hz, 6'-H), and 7.45 (1 H, d, $J = 8$ Hz, 7'-H); δ_C (22.5 MHz, $CDCl_3$) 30.93 (t, 2'- or 3'-C), 40.79 (t, 4- and 5-C), 48.49 (t, 2'- or 3'-C), 55.42 (q, -OCH₃), 72.76 (s, 1-C), 109.32 (d, 4'-C), 113.66 (d, 6'-C),

125.41 (d, 7'-C), 136.95 (s, 7a'-C), 144.0 (s, 3a'-C), and 160.09 (s, 5'-C); m/z 238 (M^+ , 34 %), 210 (38), 178 (100), and 145 (97).

2,3-Dihydro-7-methoxy-9H-1,4-dithiafluorene (110).

N-Bromosuccinimide (380 mg, 2.1 mmol) was added in three portions during 40 minutes to a mixture of 2-(5-methoxy-1-indanyl)-1,3-dithiolane (500 mg, 2.1 mmol) and benzoyl peroxide (20 mg, 0.08 mmol) in carbon tetrachloride, heated under reflux. The mixture was heated for 2 h, thin layer chromatography showed some starting material present. Additional *N*-bromosuccinimide (100 mg, 0.06 mmol) was added and the mixture heated under reflux for 1 h. The precipitated succinimide was filtered from the cooled mixture and the filtrate washed with water, saturated brine, dried ($MgSO_4$) and evaporated under reduced pressure to a brown gum. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a colourless solid (450 mg, 90 %) m.p. 83 - 85 °C (Accurate mass found: 236.0320. $C_{12}H_{12}OS_2$ requires: 236.0327.); $\nu_{max}(CHCl_3)$ 1605, and 1590 cm^{-1} (ArC-C); δ_H (100 MHz, $CDCl_3$) 3.25 (4 H, s, 2- and 3- CH_2), 3.40 (2 H, s, 9- CH_2), 3.78 (3 H, s, - OCH_3), 6.78 (1 H, dd, J = 8 Hz and 2 Hz, 6-H), 6.90 (1 H, d, J = 2 Hz, 8-H), and 7.00 (1 H, d, J = 8 Hz, 5-H) δ_C (22.5 MHz, $CDCl_3$) 26.06 (t, 2- or 3-C), 27.20 (t, 2- or 3-C), 42.31 (t, 9-C), 55.53 (q, - OCH_3), 110.03 (d, 8-C), 111.49 (d, 6-C), 116.80 (d, 5-C), 123.03 (s, 4a- or 9a-C), 124.38 (s, 4a- or 9a-C), 137.12 (s, 4b-C), 141.34 (s, 8a-C), and 157.54 (s, 7-C); m/z 236 (M^+ , 100 %), 208 (57), and 164 (46).

This compound decomposed to a dark red gum.

Attempted preparation of 2-(3'-bromo-5'-methoxy-1'-indanyl)1,3-dithiolane (109).

Boron trifluoride etherate (2 drops) was added to a stirred mixture of 3-bromo-5-methoxy-1-indanone (200 mg, 0.8 mmol) and 1,2-ethanedithiol (0.2 cm^3 ,

2.38 mmol) in dry dichloromethane (5 cm³) at 0 °C under an atmosphere of dry nitrogen. The mixture was stirred at room temperature for 16 h, diluted with dichloromethane and washed with 5 % aqueous sodium hydroxide, water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to an orange gum. Thin layer chromatographic analysis [silica; ethyl acetate - petroleum ether (1: 4)] revealed that the starting material had been consumed and that the gum contained predominantly one compound of higher R_f. Attempts to purify this product using dry column flash chromatography resulted in the decomposition of the product. This reaction was repeated on a 5.2 mmol scale which yielded an orange oil (1.7 g); δ_{H} (60 MHz, CDCl₃) 3.20 (2 H, m, 2-CH₂), 3.55 (4 H, brs, -SCH₂CH₂S-), 3.70 (3 H, s, -OCH₃), 5.30 (1 H, t, *J* = 5 Hz, 3-CHBr), 6.75 (2 H, m, 4- and 6-H), and 7.40 (1 H, d, *J* = 8 Hz, 7-H). This oil was used without further purification.

Attempted preparation of 2-[3'-1-(3"-pyridyl)ethyl-5'-methoxy-1'-indanyl]-1,3-dithiolane.

A 1.6 M solution of n-butyllithium in hexane (1 cm³, 1.58 mmol) was added dropwise to a stirred solution of dry diisopropylamine (0.22 cm³, 1.58 mmol) in dry tetrahydrofuran (5 cm³) under a dry nitrogen atmosphere at 0 °C. The reaction mixture was stirred for 0.5 h and hexamethylphosphoric triamide (0.27 cm³, 1.58 mmol) was added and the mixture stirred for a further 0.25 h. A solution of 3-ethylpyridine (0.18 cm³, 1.58 mmol) in dry tetrahydrofuran (4 cm³) was added dropwise during five minutes and the mixture stirred for 0.5 h. A solution of 2-(3'-bromo-5'-methoxy-1'-indanyl)-1,3-dithiolane (600 mg, 1.89 mmol) in dry tetrahydrofuran (5 cm³) was added dropwise during five minutes and the mixture allowed to warm to room temperature during 1.25 h. The mixture was poured onto 10 % aqueous hydrochloric acid and the organic layer separated. The aqueous layer was basified with solid potassium hydroxide and extracted with ether. The combined extracts were washed with water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to a dark red oil

(90 mg). ^1H n.m.r. showed this to be recovered 3-ethylpyridine.

The organic layer was washed with water, saturated brine, dried (MgSO_4) and evaporated under reduced pressure to a red oil. ^1H n.m.r. showed this to be recovered 2-(3-bromo-5-methoxy-1-indanyl)-1,3-dithiolane.

3,5-Dimethoxy-1-indanol.

Sodium borohydride (100 mg, 2.4 mmol) was added in portions, during 10 minutes, to a solution of 3-bromo-5-methoxy-1-indanone (500 mg, 2 mmol) in methanol (10 cm^3) at 0°C . When the addition was complete the mixture was allowed to warm to room temperature during 1.5 h, poured onto water and extracted with dichloromethane. The combined extracts were washed with water, saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to a yellow oil. (220 mg); $\nu_{\text{max}}(\text{CHCl}_3)$ 3400 br (-OH), 1605, and 1590 sh cm^{-1} (ArC-C); $\delta_{\text{H}}(60\text{ MHz, CDCl}_3)$ 2.25 (2 H, dd, $J = 6\text{ Hz}$, 2- CH_2), 2.62 (1 H, brs, exch. D_2O , -OH), 3.30 (3 H, s, 3- OCH_3), 3.72 (3 H, s, 5- OCH_3), 4.80 (1 H, t, $J = 6\text{ Hz}$, 3- CHOCH_3), 5.20 (1 H, t, $J = 6\text{ Hz}$, 1- CHOH), 6.75 (2 H, m, 4- and 6-H), and 7.15 (1 H, d, $J = 8\text{ Hz}$, 7-H). This compound was used immediately in the next step.

1-t-Butyldimethylsilyloxy-3,5-dimethoxyindan (107).

A mixture of 3,5-dimethoxy-1-indanol (220 mg, 1.13 mmol), t-butyldimethylchlorosilane (160 mg, 1.09 mmol), and imidazole (120 mg, 1.81 mmol) in *N,N*-dimethylformamide (8 cm^3) was stirred at room temperature during 20 h. The mixture was diluted with chloroform, washed with water, saturated brine, dried (MgSO_4) and evaporated to a yellow oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as an orange oil (250 mg, 74 %); $\nu_{\text{max}}(\text{CHCl}_3)$ 1601 (ArC-C), and 835 cm^{-1} (C-O-Si); $\delta_{\text{H}}(100\text{ MHz, CDCl}_3)$ 0.15 (6 H, s, - $\text{OSi}(\text{CH}_3)_2$), 0.90 (9 H, s, - $\text{OSiC}(\text{CH}_3)_3$), 2.30 (2 H, m,

2-CH₂), 3.34 (3 H, s, 3-OCH₃), 3.76 (3 H, s, 5-OCH₃), 4.80 (1 H, dd, $J = 8$ Hz and 3 Hz, 3-CHOCH₃), 5.35 (1 H, t, $J = 8$ Hz, 1-CHOSi), 6.85 (2 H, m, 4- and 6-H), and 7.20 (1 H, d, $J = 8$ Hz, 7-H). m/z (C.I.) 309 ($M^+ + 1$, 14 %), 277 (100), 251 (31), 193 (23), 177 (95), and 145 (43).

If the reduction was performed in ethanol a similar result occurred yielding 3-ethoxy-5-methoxy-1-indanol.

Attempted synthesis of 5,6-dimethoxy-1-indenone.

A mixture of 5,6-dimethoxy-1-indanone (100 mg, 0.52 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (170 mg, 0.78 mmol) in dry benzene (5 cm³) was heated under reflux, under an atmosphere of dry nitrogen for 5 h. Thin layer chromatography of the black mixture showed consumption of the starting material but no new product formation.

Attempted synthesis of 5-methoxy-1-indenone (75).

Method A.

A mixture of 3-bromo-5-methoxy-1-indanone (250 mg, 1 mmol) and dry pyridine (1 cm³, 0.012 mol) in dry ether (10 cm³) was stirred at 50 °C for 3 h. The cooled mixture was washed with saturated copper sulphate solution, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to an orange solid (200 mg). The ¹H n.m.r. spectrum showed this to be recovered 3-bromo-5-methoxy-1-indanone (80% recovery).

Method B.

A mixture of 3-bromo-5-methoxy-1-indanone (600 mg, 2.5 mmol), lithium bromide (530 mg, 6 mmol) and lithium carbonate (450 mg, 6 mmol) in dry

N,N-dimethylformamide (10 cm³) was heated at 160 °C under an atmosphere of dry nitrogen for 1 h. The cooled mixture was poured onto water and extracted with chloroform. The combined extracts were washed with water, 2 M hydrochloric acid, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to a black gum. Thin layer chromatography revealed this to be a complex mixture.

5-Methoxy-1-indenone (75).

Method B.

A mixture of 5-methoxy-1-indanone (150 mg, 0.9 mmol) and phenylselenenyl chloride (200 mg, 1.04 mmol) in ethyl acetate (10 cm³) was stirred at room temperature for 2 h. Water (5 cm³) was added and the mixture stirred for 15 minutes, then the organic layer separated. Tetrahydrofuran (5 cm³) was added followed by 30 % hydrogen peroxide (0.28 cm³, 2.5 mmol) slowly and the mixture stirred for 2 h. The mixture was washed with water, 2 M sodium carbonate solution, saturated brine, dried (Na₂SO₄) and evaporated to a pale yellow solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a yellow oil (50 mg, 35 %).

Method C.

A solution of 3-bromo-5-methoxy-1-indanone (800 mg, 3.3 mmol) in *N,N*-dimethylacetamide (25 cm³) was stirred with finely divided calcium carbonate (360 mg, 3.6 mmol) at 120 °C for 6 h. The cooled mixture was filtered through celite and the filtrate washed with saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to an orange oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 9) afforded two products: i) a yellow oil (220 mg, 42 %) which was 5-methoxy-1-indenone and ii) an orange solid which was recovered 3-bromo-5-methoxy-1-indanone (180 mg, 23 % recovery).

Method D.

1,8-Diazabicyclo[5.4.0]undec-7-ene (7.07 cm³, 0.047 mol) was added dropwise during 30 minutes to a solution of 3-bromo-5-methoxy-1-indanone (10.3 g, 0.043 mol) in dry tetrahydrofuran (125 cm³) at -10 °C under an atmosphere of dry nitrogen. When the addition was complete the mixture was stirred for ten minutes then quenched with 1 M sulphuric acid (40 cm³), allowed to warm to room temperature and extracted with ether. The combined extracts were washed with saturated brine, dried (MgSO₄) and evaporated under reduced pressure to an orange oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 9) afforded the title compound as a yellow oil (5.9 g, 85 %).

4- And 6-bromo-5-methoxy-1-indanone (115 and 116).

Bromine (0.16 cm³, 3.1 mmol) was added, during ten minutes, to a solution of 5-methoxy-1-indanone (500 mg, 3.1 mmol) in glacial acetic acid (10 cm³). When the addition was complete the mixture was stirred at room temperature for 1.5 h, diluted with water and extracted with dichloromethane. The combined extracts were washed with water, saturated aqueous sodium bicarbonate, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to an orange oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4 - 1:1) afforded three products: i) a yellow solid (400 mg); ν_{\max} (CHCl₃) 1690 (C=O), and 1590 cm⁻¹ (ArC-C); δ_{H} (60 MHz, CDCl₃) 1.75 (2 H, m, 2-CH₂), 3.10 (2 H, m, 3-CH₂), 4.00 (3 H, s, -OCH₃), 6.95 (1 H, d, J = 8 Hz, 6-H), and 7.75 (1 H, d, J = 8 Hz, 7-H); ii) a yellow solid (340 mg) ¹H n.m.r. showed this to be recovered 5-methoxy-1-indanone (68 % recovery); and iii) a pale yellow solid (100 mg); m.p. 146 - 148 °C (Accurate mass found: 239.9801 and 241.9785. C₁₀H₉O₂Br requires 239.9784 and 241.9764.); ν_{\max} (CHCl₃) 1690 (C=O), and 1590 cm⁻¹ (ArC-C); δ_{H} (100 MHz, CDCl₃) 2.70 (2 H, m, 2-CH₂), 3.12 (2 H, m, 3-CH₂), 4.00 (3 H, s, -OCH₃), 6.98 (1 H, s, 4-H), and 7.95 (1 H, s, 7-H); δ_{C} (67.8 MHz, CDCl₃) 25.80 (t, 3-C), 36.43 (t, 2-C), 56.58

(q, -OCH₃), 108.43 (d, 4-C), 112.34 (s, 6-C), 128.51 (d, 7-C), 131.09 (s, 7a-C), 156.91 (s, 3a-c), 160.72 (s, 5-C), and 240.0 (s, 1-C); *m/z* 242 (*M*⁺, 92 %), 240 (*M*⁺, 100), 214 (26), 212 (26), and 162(23).

2-Bromo-5-methoxy-1-indanone (120).

A solution of 5-methoxy-1-indanone (5.5 g, 0.034 mol) in dry tetrahydrofuran (30 cm³) was added, *via* a cannula during 15 minutes, to a solution of phenyltrimethylammonium tribromide (12.78 g, 0.034 mol) in dry tetrahydrofuran (20 cm³) at 0 °C under an atmosphere of dry nitrogen. The mixture was stirred at 0 °C for 30 minutes, then at room temperature for 16 h, poured onto saturated aqueous sodium bicarbonate and extracted with ether. The combined extracts were washed with water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to a brown solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4 - 1: 1) afforded the title compound as a yellow solid (4.53 g, 55 %). ν_{max} (CHCl₃) 1705 (C=O), and 1595 cm⁻¹ (ArC-C); δ_{H} (60 MHz, CDCl₃) 3.65 (2 H, m, 3-CH₂), 3.94 (3 H, s, -OCH₃), 4.68 (1 H, dd, *J* = 8 Hz and 3 Hz, 2-CHBr), 6.95 (1 H, s, 4-H), 7.02 (1 H, dd, *J* = 8 Hz and 2 Hz, 6-H), and 7.80 (1 H, d, *J* = 8 Hz, 7-H).

Attempted synthesis of 5-methoxy-1-indenone (75).

Method C.

1,8-Diazabicyclo[5.4.0]undec-7-ene (0.14 cm³, 0.96 mmol) was added dropwise to a solution of 2-bromo-5-methoxy-1-indanone (210 mg, 0.87 mmol) in dry tetrahydrofuran (5 cm³) at -10 °C under an atmosphere of dry nitrogen. The mixture was stirred for 15 minutes and the black solution quenched with 2 M sulphuric acid (3 cm³), warmed to room temperature and extracted with ether. The combined extracts were washed with water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to an orange solid (189 mg). ¹H n.m.r. showed that this was

recovered 2-bromo-5-methoxy-1-indanone (86 % recovery).

6-Methoxy-1,4-dimethyl-1,4,4a,9a-tetrahydro-9-fluorenone (114).

Method A.

A mixture of 5-methoxy-1-indenone (1.06 g, 6.6 mmol) and *trans*-2-*trans*-4-hexadiene (0.75 g, 9.13 mmol) in chloroform (10 cm³) was heated under reflux for 48 h, cooled and the solvent evaporated under reduced pressure to an orange gum. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a pale yellow solid (0.78 g, 49 %) m.p. 110 - 112 °C (colourless needles from petroleum ether). (Found: C, 79.15; H, 7.5. C₁₆H₁₈O₂ requires C, 79.3; H, 7.5 %); ν_{\max} (NUJOL) 1685 (C=O), 1595 (ArC-C), and 1255 cm⁻¹ (C-O-C); δ_{H} (270 MHz, CDCl₃) 1.37 (3 H, d, J = 7 Hz, -CH₃), 1.56 (3 H, d, J = 7 Hz, -CH₃), 2.45 (2 H, brm, 1- and 4-H), 2.84 (1 H, dd, J = 7 Hz and 7 Hz, 9a-H), 3.61 (1 H, dd, J = 7 Hz and 7 Hz, 4a-H), 3.86 (3 H, s, -OCH₃), 5.30 (1 H, ddd, J = 9 Hz, 3 Hz and 3 Hz, 2- or 3-H), 5.64 (1 H, ddd, J = 9 Hz, 3 Hz and 3 Hz, 2- or 3-H), 6.87 (1 H, dd, J = 8 Hz and 2 Hz, 7-H), 6.95 (1 H, d, J = 2 Hz, 5-H), and 7.59 (1 H, d, J = 8 Hz, 8-H); δ_{C} (67.8 MHz, CDCl₃) 16.73 (q, -CH₃), 17.90 (q, -CH₃), 32.20 (d, 1- or 4-C), 32.73 (d, 1- or 4-C), 44.65 (d, 4a-C), 52.66 (d, 9a-C), 55.43 (q, -OCH₃), 111.46 (d, 5 or 7-C), 114.72 (d, 5 or 7-C), 124.38 (d, 8-C), 132.60 (d, 2- or 3-C), 133.04 (s, 8a-C), 134.86 (d, 2- or 3-C), 156.58 (s, 4b-C), 164.08 (s, 6-C), and 206.06 (s, 9-C); m/z 242 (M^+ , 51 %), 161 (100) and 160 (89).

Method B.

A mixture of 5-methoxy-1-indenone (1.1 g, 6.9 mmol), *trans*-2-*trans*-4-hexadiene (1.12 g, 0.013 mol) and zinc iodide (300 mg, 0.9 mmol) in dry dichloromethane (20 cm³) was stirred at 50 °C, under an atmosphere of dry nitrogen, for 5 h, then at room temperature for 16 h. The mixture was diluted with dichloromethane, washed with 0.1 M sodium thiosulphate solution, saturated brine,

dried (Na_2SO_4) and evaporated under reduced pressure to a yellow solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a pale yellow solid (1.06 g, 64 %).

Method C.

Boron trifluoride etherate (0.4 cm^3 , 3.6 mmol) was added dropwise to a solution of 5-methoxy-1-indenone (5.7 g, 0.036 mol) in dry dichloromethane (60 cm^3) under an atmosphere of dry nitrogen at -78°C and the mixture stirred for 5 minutes. *Trans-2-trans-4-hexadiene* (5 cm^3 , 0.044 mol) was added, dropwise during 10 minutes, and the mixture allowed to warm to room temperature over 16 h. The mixture was diluted with water and extracted with dichloromethane. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to an orange solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a pale yellow solid (6.85 g, 79 %).

Attempted sodium cyanoborohydride reduction of 6-methoxy-1,4-dimethyl-1,4,4a,9a-tetrahydro-9-fluorenone.

Sodium cyanoborohydride (250 mg, 4 mmol) was added to a stirred mixture of 6-methoxy-1,4-dimethyl-1,4,4a,9a-tetrahydro-9-fluorenone (150 mg, 0.6 mmol) and bromocresol green (5 mg) in dry methanol (6 cm^3). The yellow colour was restored from blue by dropwise addition of 2 M hydrochloric acid and maintained by occasional subsequent additions during 4 h. The solvent was evaporated under reduced pressure and the residue taken up in water, saturated with sodium chloride and extracted with ether. The combined extracts were washed with saturated brine, dried (MgSO_4) and evaporated under reduced pressure to a pale cream solid (180 mg). ^1H n.m.r. and i.r. analysis showed that this was predominantly recovered starting material.

9-Hydroxy-6-methoxy-1,4-dimethyl-1,4,4a,9a-tetrahydrofluorene (121).

A solution of 6-methoxy-1,4-dimethyl-1,4,4a,9a-tetrahydro-9-fluorenone (475 mg, 1.96 mmol) in dry ether (10 cm³) was added dropwise to a stirred suspension of lithium aluminium hydride (50 mg, 1.32 mmol) in dry ether (3 cm³) at such a rate so as to maintain gentle reflux. When the addition was complete the mixture was heated under reflux for 0.5 h, cooled and the excess hydride destroyed by cautious addition of wet ether. The mixture was poured onto 38 % aqueous potassium, sodium tartrate solution and extracted with ether. The combined extracts were washed with water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to a colourless oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as two products: i) a colourless solid (308 mg) R_F = 0.58 m.p. 60 - 61.5 °C (petroleum ether); (Found: C, 78.2; H, 8.3. C₁₆H₂₀O₂ requires C, 78.65; H, 8.25 %); λ_{max}(EtOH) 202, 225, and 278 nm; ν_{max}(CHCl₃) 3550 (-OH), and 1600 cm⁻¹ (ArC-C); δ_H(270 MHz, CDCl₃) 1.01 (3 H, d, *J* = 8 Hz, -CH₃), 1.39 (3 H, d, *J* = 7 Hz, -CH₃), 1.66 (1 H, d, *J* = 10 Hz, exch. D₂O, -OH), 2.68 (3 H, brm, 1-, 4-, and 9a-H), 3.56 (1 H, dd, *J* = 9 Hz and 9 Hz, 4a-H), 3.80 (3 H, s, -OCH₃), 4.93 (1 H, dd, *J* = 10 Hz and 7 Hz, 9-H), 5.50 (1 H, ddd, *J* = 9 Hz, 3 Hz, and 3 Hz, 2- or 3-H), 5.94 (1 H, ddd, *J* = 9 Hz, 3 Hz and 3 Hz, 2- or 3-H), 6.79 (1 H, dd, *J* = 9 Hz and 2 Hz, 7-H), 6.80 (1 H, s, 5-H), and 7.31 (1 H, d, *J* = 9 Hz, 8-H); *m/z* 244 (*M*⁺, 11 %), 226 (10), 173 (100), 162 (59), and 147 (26). and ii) a colourless solid (128 mg) R_F = 0.33; ν_{max} (CHCl₃) 3580, 3450 br (-OH), and 1600 cm⁻¹ (ArC-C); δ_H(270 MHz, CDCl₃) 1.02 (3 H, d, *J* = 7 Hz, -CH₃) 1.35 (3 H, d, *J* = 7 Hz, -CH₃), 1.86 (1 H, s, exch. D₂O, -OH), 2.45 (3 H, brm, 1-, 4- and 9a-H), 3.55 (1 H, dd, *J* = 8 Hz, and 8 Hz, 4a-H), 3.78 (3 H, s, -OCH₃), 4.93 (1 H, d, *J* = 6 Hz, 9-H), 5.60 (2 H, s, 2- and 3-H), 6.74 (1 H, d, *J* = 2 Hz, 5-H), 6.78 (1 H, dd, *J* = 8 Hz and 2 Hz, 6-H), and 7.20 (1 H, d, *J* = 8 Hz, 7-H). The yield of both products = 91 %. The R_F of the starting material is 0.52, on silica eluting with ethyl acetate - petroleum ether (1: 4).

The same result was achieved by heating the adduct under reflux for 6 hours in wet methanol with sodium borohydride followed by the usual work - up.

6-Methoxy-1,4-dimethyl-4,4a-dihydro-1H-fluorene (122).

A solution of 9-hydroxy-6-methoxy-1,4-dimethyl-1,4,4a,9a-tetrahydrofluorene (100 mg, 0.4 mmol) in tetrahydrofuran (8 cm³) was stirred with 5 M sulphuric acid (1.5 cm³) at 80 °C for 2 h. The cooled mixture was poured onto ice and extracted with hexane. The combined extracts were washed with saturated aqueous sodium bicarbonate, water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to a pale yellow oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 5) afforded the title compound as a pale yellow oil (80 mg, 88 %). λ_{max} (EtOH) 213, 269, and 276 (sh) nm; ν_{max} (Neat) 1600, and 1575 cm⁻¹ (ArC-C); δ_{H} (60 MHz, CDCl₃) 0.38 (3 H, d, J = 7 Hz, 4-CH₃) 1.30 (3 H, d, J = 7 Hz, 1-CH₃), 3.0 (2 H, brm, 1- and 4-H), 3.50 (1 H, d, J = 8 Hz, 4a-H), 3.75 (3 H, s, -OCH₃), 5.52 (1 H, dd, J = 10 Hz and 3 Hz, 2-H), 5.85 (1 H, ddd, J = 10 Hz, 5 Hz, and 3 Hz, 3-H), 6.45 (1 H, brs, 9-H), 6.75 (1 H, dd, J = 8 Hz and 2 Hz, 7-H), 6.90 (1 H, brs, 5-H), and 7.15 (1 H, d, J = 8 Hz, 8-H). This was used immediately in the next step.

6-Methoxy-1,4-dimethyl-9-fluorenone (35).

Method A.

A mixture of 6-methoxy-1,4-dimethyl-4,4a-dihydro-1H-fluorene (80 mg, 0.35 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1 g, 4.4 mmol) in dry benzene (10 cm³) was heated under reflux for 2.5 h under an atmosphere of dry nitrogen. The cooled mixture was diluted with petroleum ether (b.p. 40 - 60 °C), the precipitated quinol filtered, washed with hot petroleum ether and the filtrate concentrated *in vacuo*. Chromatography on neutral alumina eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a pale yellow solid (30 mg, 36 %), m.p. 144 - 5 °C (EtOAc / Pet. ether) (lit., ⁴⁰ 125 - 6 °C); (Found: C, 80.6; H, 6.0. Calc. for C₁₆H₁₄O₂: C, 80.65; H, 5.9 %); λ_{max} (EtOH) 254 (ϵ 29 100 dm³ mol⁻¹ cm⁻¹), 274 (30 220), 295 (5 820), and 308 nm (6 340); ν_{max} (CHCl₃) 1690 (C=O), 1600, and 1580 cm⁻¹

(ArC-C); δ_{H} (270 MHz, CDCl_3) 2.43 (3 H, s, Ar- CH_3), 2.54 (3 H, s, Ar- CH_3), 3.85 (3 H, s, - OCH_3), 6.64 (1 H, dd, $J = 8$ Hz and 2 Hz, 7-H), 6.87 (1 H, d, $J = 8$ Hz, 2-H), 6.99 (1 H, d, $J = 2$ Hz, 5-H), 7.0 (1 H, d, $J = 8$ Hz, 3-H), and 7.53 (1 H, d, $J = 8$ Hz, 8-H); δ_{C} (67.8 MHz, CDCl_3) 17.52 (q, - CH_3), 19.93 (q, - CH_3), 55.59 (q, - OCH_3), 110.90 (d, 5- or 7-C), 110.93 (d, 5- or 7-C), 125.44 (d, 8-C), 127.78 (s, 8a-C), 130.91 (s, 4-C), 131.78 (d, 2-C), 132.0 (s, 1-C), 136.26 (d, 3-C), 136.31 (s, 9a-C), 141.14 (s, 4b-C), 146.70 (s, 4a-C), 164.64 (s, 6-C), and 193.96 (s, 9-C); m/z 238 (M^+ , 100 %), and 195 (26).

Method B.

A mixture of 6-methoxy-1,4-dimethyl-1,4,4a,9a-tetrahydro-9-fluorenone (800 mg, 3.3 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.87 g, 8 mmol) in dry benzene (20 cm^3) was heated under reflux, under an atmosphere of dry nitrogen, for 4.5 h. The cooled mixture was diluted with petroleum ether, the precipitated hydroquinone filtered off and the filtrate concentrated *in vacuo*. Chromatography on neutral alumina eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a pale yellow solid (400 mg, 51 %).

Method C.

A solution of 6-methoxy-1,4-dimethyl-1,4,4a,9a-tetrahydro-9-fluorenone (60 mg, 0.25 mmol) in diglyme (10 cm^3) was heated under reflux with 10 % palladium on charcoal (18 mg) and nitrogen passed through the mixture for 6 h. The cooled mixture was diluted with ethyl acetate and filtered through celite. The filtrate was washed with water, saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to a yellow solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 9) afforded the title compound as a pale yellow solid (50 mg, 84 %).

6-Methoxy-1,4-dimethylfluorene (33).

Method A.

A mixture of 6-methoxy-1,4-dimethyl-9-fluorenone (1.4 g, 5.9 mmol) and 99 % hydrazine hydrate (10 cm³) in freshly distilled 1,2-ethanediol (100 cm³) was heated under reflux for 4 h. The cooled mixture was extracted with dichloromethane and the combined extracts washed with water, 2 M hydrochloric acid, water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to give an orange solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 9) afforded the title compound as a colourless solid (960 mg, 73 %). m.p. 101.5 - 102.4 °C (petroleum ether). (Found: C, 85.6; H, 7.2. C₁₆H₁₆O requires C, 85.7; H, 7.2 %); λ_{max} (EtOH) 216 (ϵ 36 720 dm³ mol⁻¹ cm⁻¹), 262 (12 560), 270 (12 330), 297 (7 290), and 308 nm (6 840); ν_{max} (CHCl₃) 1600, and 1580 cm⁻¹ (ArC-C); δ_{H} (270 MHz, CDCl₃) 2.32 (3 H, s, Ar-CH₃), 2.64 (3 H, s, Ar-CH₃), 3.60 (2 H, s, 9-CH₂), 3.84 (3 H, s, -OCH₃), 6.82 (1 H, dd, J = 8 Hz and 2 Hz, 7-H), 6.97 (1 H, d, J = 7.5 Hz, 2- or 3-H), 7.02 (1 H, d, J = 7.5 Hz, 2- or 3-H), 7.39 (1 H, d, J = 8 Hz, 8-H), and 7.43 (1 H, d, J = 2 Hz, 5-H); δ_{C} (22.5 MHz, CDCl₃) 18.26 (q, -CH₃), 20.37 (q, -CH₃), 34.99 (t, 9-C), 55.26 (q, -OCH₃), 109.05 (d, 5-C), 111.0 (d, 7-C), 124.82 (d, 2- or 3-C), 127.20 (d, 2- or 3-C), 128.99 (d, 8-C), 130.13 (s, 4-C), 131.05 (s, 8a-C), 135.49 (s, 1-C), 138.90 (s, 4b-C), 143.18 (s, 4a-C), 144.10 (s, 9a-C), and 158.62 (s, 6-C), the assignments for 4a, 4b, and 9a are interchangeable; m/z 224 (M^+ , 90 %), 209 (100, M -CH₃).

Method B.

A solution of 6-methoxy-1,4-dimethyl-1,4,4a,9a-tetrahydro-9-fluorenone (6.04 g, 0.025 mol) in dry tetrahydrofuran (60 cm³) was reduced using lithium aluminium hydride (500 mg, 0.013 mol) by the normal procedure (page 109) to give 9-hydroxy-6-methoxy-1,4,-dimethyl-1,4,4a,9a-tetrahydrofluorene (121) as a mixture of two isomers (7 g). The crude mixture was treated with 5 M sulphuric acid (15 cm³)

by the normal procedure (page 110) to give, after chromatography, 6-methoxy-1,4-dimethyl-4,4a-dihydro-1*H*-fluorene (5.18 g) (122).

The dihydrofluorene was dissolved in freshly distilled diglyme (40 cm³) and heated under reflux with 10 % palladium on charcoal (800 mg), with nitrogen passed through the mixture, for 2 h. The cooled mixture was diluted with ethyl acetate and filtered through celite. The filtrate was washed with water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as an off - white solid (4.8 g, 93 %). 86 % Overall from the starting adduct.

Attempted synthesis of 1,4-dimethyl-6-methoxyfluorene-7-carbaldehyde (125).

Freshly distilled phosphorus oxychloride (0.05 cm³, 0.59 mmol) was added slowly to dry *N,N*-dimethylformamide (3 cm³) at 0 °C under an atmosphere of dry nitrogen and the mixture stirred for 0.5 h. A solution of 6-methoxy-1,4-dimethylfluorene (80 mg, 0.35 mmol) in dry *N,N*-dimethylformamide (1 cm³) was added dropwise and the mixture warmed to room temperature during 1 h. Thin layer chromatographic analysis revealed no change and the mixture was heated under reflux for 5 h, cooled and diluted with water. The mixture was extracted with chloroform and the combined extracts dried (MgSO₄) and evaporated under reduced pressure to afford a pale brown solid (75 mg). The product showed an identical ¹ H n.m.r. spectrum to 6-methoxy-1,4-dimethylfluorene.

1,4-Dimethyl-6-methoxyfluorene-7-carbaldehyde (125).

A mixture of 6-methoxy-1,4-dimethylfluorene (100 mg, 0.4 mmol), phosphorus oxychloride (0.07 cm³, 0.8 mmol) and *N*-methylformanilide (0.11 cm³, 0.9 mmol) in 1,2-dichlorobenzene (8 cm³) was stirred at 90 °C, under an atmosphere of dry nitrogen, for 1.5 h. The cooled mixture was poured onto saturated aqueous sodium acetate and extracted with ethyl acetate. The combined extracts were washed

with water, saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to give an orange oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 9) afforded two products: i) A colourless solid, ^1H n.m.r. showed this to be recovered starting material (74 mg, 74 % recovery) and ii) The title compound as a pale cream solid (21 mg, 21 %). m.p. 168.7 - 169.5 °C. (Accurate mass found: 252.1131. $\text{C}_{17}\text{H}_{16}\text{O}_2$ requires 252.1148.); λ_{max} (EtOH) 208, 225 (sh), 306, and 348 nm; ν_{max} (CHCl_3) 1665 (C=O), 1605, and 1585 cm^{-1} (ArC-C); δ_{H} (100 MHz, CDCl_3) 2.28 (3 H, s, Ar- CH_3), 2.61 (3 H, s, Ar- CH_3), 3.46 (2 H, s, 9- CH_2), 3.91 (3 H, s, - OCH_3), 7.05 (2 H, s, 2- and 3-H), 7.30 (1 H, s, 5-H), 7.85 (1 H, s, 8-H), and 10.48 (1 H, s, -CHO); δ_{C} (22.5 MHz, CDCl_3) 18.42 (q, - CH_3), 20.64 (q, - CH_3), 35.05 (t, 9-C), 55.69 (q, - OCH_3), 105.86 (d, 5-C), 122.22 (s, 7-C), 123.57 (d, 8-C), 128.99 (d, 2- or 3-C), 129.53 (d, 2- or 3-C), 131.26 (s, 4-C), 135.22 (s, 1-C), 138.14 (s, 8a-C), 144.81 (s, 4a- and 9a-C), 150.44 (s, 4b-C), 161.66 (s, 6-C), and 189.61 (d, -CHO); m/z 252 (M^+ , 100 %), 237 (41), 223 (93), 209 (36) and 165 (26).

Attempted preparation of 6-hydroxy-1,4-dimethylfluorene (126).

Iodotrimethylsilane (0.11 cm^3 , 0.75 mmol) was added to a solution of 6-methoxy-1,4-dimethylfluorene (130 mg, 0.6 mmol) in dry chloroform (5 cm^3) under an atmosphere of dry nitrogen and the mixture stirred at 55 °C for 22 h. The cooled mixture was poured onto methanol and the combined organics evaporated under reduced pressure to an orange solid. The solid was dissolved in ether and washed with 1 M sodium bisulphite, saturated aqueous sodium bicarbonate, saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to a colourless solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded two products: i) a colourless solid (50 mg) ^1H n.m.r. and i.r. showed this to be recovered starting material (39 % recovery), and ii) a colourless solid (11 mg), ^1H n.m.r. and i.r. showed this to be the title compound 9 %.

1,4-Dimethyl-6-phenylsulphonyloxyfluorene (127).

6-Methoxy-1,4-dimethylfluorene (2.45 g, 11 mmol) was added to dry pyridinium hydrochloride (10 g, 0.1 mol) at 150 °C. The temperature was raised to 220 °C and the mixture stirred under an atmosphere of dry nitrogen for 2 h. The cooled mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with 2 M hydrochloric acid, 3 % aqueous sodium bicarbonate, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to afford 6-hydroxy-1,4-dimethylfluorene as a pale brown solid (3 g). $\nu_{\max}(\text{CHCl}_3)$ 3320 (-OH), 1600, and 1580 cm⁻¹ (ArC-C); $\delta_{\text{H}}(60 \text{ MHz, CDCl}_3)$ 2.35 (3 H, s, Ar-CH₃), 2.65 (3 H, s, Ar-CH₃), 3.68 (2 H, s, 9-CH₂), 6.76 (1 H, dd, $J = 8 \text{ Hz}$ and 2 Hz , 7-H), 7.04 (2 H, s, 2- and 3-H), 7.24 - 7.45 (3 H, m, 5-, 8-H, and Ar-OH).

The fluorene was dissolved in dry pyridine (20 cm³) and stirred at 0 °C. A solution of freshly distilled benzenesulphonyl chloride (1.7 cm³, 13 mmol) in dry pyridine (4 cm³) was added dropwise during five minutes and the mixture allowed to warm to room temperature during 16 h. After stirring at 50 °C for 3 h the cooled mixture was diluted with water (5 cm³) and concentrated *in vacuo*. The residue was extracted with dichloromethane and the combined extracts washed with 50 % aqueous hydrochloric acid, water, saturated aqueous copper sulphate, water, 2 M sodium hydroxide, water, dried (Na₂SO₄) and evaporated under reduced pressure to an orange gum. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a colourless solid (2.89 g, 75 %) m.p. 104 - 104.5 °C (ethyl acetate / petroleum ether). (Found: C, 72.1; H, 5.2. C₂₁H₁₈O₃S requires C, 72.0; H, 5.2 %); $\lambda_{\max}(\text{EtOH})$ 211 (ϵ 66 230 dm³ mol⁻¹ cm⁻¹), 266 (25 000), 286 (12 280), and 297 nm (9 650); $\nu_{\max}(\text{CHCl}_3)$ 1605, 1580 (ArC-C), 1365, and 1140 cm⁻¹ (ArSO₂-OAr); $\delta_{\text{H}}(270 \text{ MHz, CDCl}_3)$ 2.30 (3 H, s, Ar-CH₃), 2.37 (3 H, s, Ar-CH₃), 3.61 (2 H, s, 9-CH₂), 6.93 (1 H, dm, $J = 8 \text{ Hz}$, 7-H), 6.99 (2 H, s, 2- and 3-H), 7.28 (1 H, brs, 5-H), 7.41 (1 H, d, $J = 8 \text{ Hz}$, 8-H), 7.48 (2 H, dd, $J = 8 \text{ Hz}$ and 8 Hz , 3'- and 5'-H), 7.63 (1 H, t, $J = 8 \text{ Hz}$, 4'-H), and 7.85 (2 H, d, $J = 8 \text{ Hz}$, 2'- and 6'-H); $\delta_{\text{C}}(67.8 \text{ MHz, CDCl}_3)$ 18.47 (q, -CH₃), 20.22 (q, -CH₃),

35.50 (t, 9-C), 116.78 (d, 5-C), 119.70 (d, 7-C), 125.36 (d, 2- or 3-C), 128.07 (d, 2- or 3-C), 128.64 (d, 2'- and 6'-C), 129.09 (d, 3'- and 5'-C), 129.34 (d, 8-C), 130.47 (s, 4-C), 131.44 (s, 1-C), 134.12 (d, 4'-C), 135.37 (s, 1'-C), 142.16 (s, 8a- and 4b-C), 142.88 (s, 4a- and 9a-C), and 148.62 (s, 6-C); m/z 350 (M^+ , 56 %), 209 (100), and 165 (26).

Attempted formylation of 1,4-dimethyl-6-phenylsulphonyloxyfluorene.

A mixture of 1,4-dimethyl-6-phenylsulphonyloxyfluorene (140 mg, 0.4 mmol), *N*-methylformanilide (0.09 cm³, 0.8 mmol) and freshly distilled phosphorus oxychloride (0.06 cm³, 0.6 mmol), in 1,2-dichlorobenzene (5 cm³) was stirred at 90 °C under an atmosphere of dry nitrogen for 28 h. The cooled mixture was poured onto saturated aqueous sodium acetate and extracted with ethyl acetate. The combined extracts were washed with water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to an orange oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded a colourless solid (112 mg). ¹H n.m.r. showed this to be recovered starting material (80 % recovery).

2-Chloromethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (129).

A mixture of 1,4-dimethyl-6-phenylsulphonyloxyfluorene (1.8 g, 5.2 mmol), concentrated hydrochloric acid (25 cm³), and 40 % aqueous formaldehyde solution (10 cm³) in glacial acetic acid (100 cm³) was stirred at 80 °C for 3.5 h. Additional formaldehyde was added (5 cm³) and the mixture stirred for 1 h, cooled and diluted with water. The mixture was extracted with chloroform and the combined extracts washed with saturated aqueous sodium bicarbonate, water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to a pale brown solid. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1: 4) afforded the title compound as a colourless solid (1.87 g, 91 %) m.p. 181.6 - 182.7 °C (ethyl acetate /

petroleum ether). (Found: C, 66.3; H, 4.8. $C_{22}H_{19}O_3SCl$ requires C, 66.2; H, 4.8 %); $\lambda_{\max}(\text{EtOH})$ 210, 265, 288 sh, and 296 nm; $\nu_{\max}(\text{CHCl}_3)$ 1605, 1585 (ArC-C), 1365, and 1140 cm^{-1} (ArSO₂-OAr); $\delta_{\text{H}}(270\text{ MHz, CDCl}_3)$ 2.38 (3 H, s, Ar-CH₃), 2.39 (3 H, s, Ar-CH₃), 3.71 (2 H, s, 9-CH₂), 4.65 (2 H, s, -CH₂Cl), 6.96 (1 H, dd, $J = 8\text{ Hz}$ and 2 Hz , 7-H), 7.07 (1 H, s, 3-H), 7.28 (1 H, d, $J = 2\text{ Hz}$, 5-H), 7.44 (1 H, d, $J = 8\text{ Hz}$, 8-H), 7.51 (2 H, dd, $J = 8\text{ Hz}$ and 8 Hz , 3'- and 5'-H), 7.66 (1 H, t, $J = 8\text{ Hz}$, 4'-H), and 7.85 (2 H, d, $J = 8\text{ Hz}$, 2'- and 6'-H); $\delta_{\text{C}}(67.8\text{ MHz, CDCl}_3)$ 14.74 (q, -CH₃), 20.15 (q, -CH₃), 36.08 (t, 9-C), 44.96 (t, -CH₂Cl), 117.07 (d, 5-C), 120.21 (d, 7-C), 125.52 (d, 3- or 8-C), 128.72 (d, 2'- and 6'-C), 129.21 (d, 3'- and 5'-C), 130.83 (s, 4-C), 131.43 (d, 8-C), 134.19 (d, 4'-C), 134.35 (s, 1'-C), 135.60 (s, 1- and 2-C), 142.53 (s), 143.89 (s), and 144.27 (s), (4a-, 4b-, 8a-, and 9a-C), and 148.82 (s, 6-C); m/z 400 (M^+ , 4 %), 398 (M^+ , 11), 362 (53), and 221 (100).

2-Cyanomethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (130).

Method A.

A solution of 2-chloromethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (53 mg, 0.13 mmol) in dry dimethyl sulphoxide (2 cm³) was added to a stirred suspension of sodium cyanide (7 mg, 0.15 mmol) in dry dimethyl sulphoxide (2.5 cm³) at 90 °C and the mixture allowed to cool to room temperature, diluted with water and extracted with chloroform. The combined extracts were washed with water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to a brown oil. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (2: 3) afforded the title compound as a pale cream solid (32 mg, 60 %) m.p. 166.8 - 167 °C (ethyl acetate / petroleum ether). (Found: C, 71.5; H, 5.1; N, 3.6. $C_{23}H_{19}NO_3S$ requires C, 71.0; H, 4.9; N, 3.6 %); $\lambda_{\max}(\text{EtOH})$ 203 (ϵ 68 340 dm³ mol⁻¹ cm⁻¹), 217 sh, 268 (11 490), 285 infl, and 295 nm (3 700); $\nu_{\max}(\text{CHCl}_3)$ 2250 (-CN), 1605, 1585 (ArC-C), 1365, and 1140 cm^{-1} (ArSO₂-OAr); $\delta_{\text{H}}(270\text{ MHz, CDCl}_3)$ 2.27 (3 H,

s, Ar-CH₃), 2.36 (3 H, s, Ar-CH₃), 3.63 (2 H, s, -CH₂CN), 3.67 (2 H, s, 9-CH₂), 6.92 (1 H, dm, *J* = 8 Hz, 7-H), 7.07 (1 H, s, 3-H), 7.24 (1 H, brs, 5-H), 7.42 (1 H, d, *J* = 8 Hz, 8-H), 7.53 (2 H, dd, *J* = 8 Hz and 8 Hz, 3'- and 5'-H), 7.68 (1 H, t, *J* = 8 Hz, 4-H), and 7.84 (2 H, d, *J* = 8 Hz, 2'- and 6'-H); δ_{C} (67.8 MHz, CDCl₃) 14.72 (q, -CH₃), 19.70 (q, -CH₃), 21.20 (t, -CH₂CN), 35.52 (t, 9-C), 116.45 (d, 5-C), 117.52 (s, -CH₂CN), 119.71 (d, 7-C), 125.13 (s, 3-C), 126.80 (s, 2-C), 128.18 (d, 2'- and 6'-C), 128.84 (d, 3'- and 5'-C), 129.25 (s, 4-C), 129.55 (d, 8-C), 130.59, (s, 1-C), 133.95 (d, 4'-C), 134.79 (s, 1'-C), 137.79 (s, 4a- or 4b-C), 141.81 (s, 4b- or 4a-C), 143.19 (s, 8a-C), 143.73 (s, 9a-C), and 148.20 (s, 6-C); *m/z* 389 (*M*⁺, 18 %), 248 (25), 149 (44), and 57 (100).

Method B.

A solution of 2-chloromethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (1.8 g, 4.5 mmol) in dry dimethyl sulphoxide (20 cm³) was added, during 10 minutes, to a stirred suspension of sodium cyanide (255 mg, 5.2 mmol) in dry dimethyl sulphoxide (5 cm³) at room temperature. The mixture was stirred for 30 minutes, quenched with water and extracted with chloroform. The combined extracts were washed with water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to an orange gum. Dry column flash chromatography eluting with ethyl acetate - petroleum ether (1:1) afforded the title compound as a pale cream solid (1.6 g, 90 %).

Attempted preparation of 2-(2-aminoethyl)-1,4-dimethyl-6-phenylsulphonyloxyfluorene (131).

A solution of 2-cyanomethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (200 mg, 0.56 mmol) in dry tetrahydrofuran (4 cm³) was added dropwise to a stirred suspension of lithium aluminium hydride (50 mg, 1.3 mmol) in dry tetrahydrofuran (5 cm³) and the mixture heated under reflux for 1 h. The cooled mixture was treated

with wet ether then poured onto 38 % potassium sodium tartrate solution (10 cm³) and extracted with ethyl acetate. The combined extracts were washed with water, dried (Na₂SO₄) and evaporated under reduced pressure to an insoluble brown solid. No further examination was made of this product.

2-(2-Aminoethyl)-1,4-dimethyl-6-phenylsulphonyloxyfluorene (131).

A solution of 2-cyanomethyl-1,4-dimethyl-6-phenylsulphonyloxyfluorene (878 mg, 2.25 mmol) in dry tetrahydrofuran (25 cm³) was added to a 1 M solution of borane-tetrahydrofuran complex (2.9 cm³, 2.9 mmol), diluted with dry tetrahydrofuran (5 cm³), and the mixture stirred at 80 - 90 °C for 24 h. Concentrated hydrochloric acid (3 cm³) was added to the cooled mixture and the tetrahydrofuran removed *in vacuo*.

The residue was taken up in water, basified with 3 M aqueous sodium hydroxide and extracted with ethyl acetate. The combined extracts were washed with water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to a colourless solid.

Chromatography on basic alumina eluting with methanol - chloroform (2: 98) afforded the title compound as a pale cream solid (495 mg, 56 %) m.p. 238 - 240 °C.

$\nu_{\max}(\text{CHCl}_3)$ 3360, 3200 (-NH₂), 1605, 1580 (ArC-C), 1360, and 1140 cm⁻¹

(ArSO₂-OAr); $\delta_{\text{H}}(60 \text{ MHz, CDCl}_3)$ 1.98 (2 H, s, *exch.* D₂O, -NH₂), 2.28 (3 H, s, Ar-CH₃), 2.38 (3 H, s, Ar-CH₃), 2.84 (4 H, brs, -CH₂CH₂NH₂), 3.68 (2 H, s, 9-CH₂), 6.88 (1 H, dd, *J* = 8 Hz and 2 Hz, 7-H), 6.90 (1 H, s, 3-H), 7.30 (2 H, m, 5- and 8-H), 7.65 (2 H, m, 2'- and 6'-H), 7.80 (1 H, m, 4'-H), and 7.90 (2 H, m, 3'- and 5'-H); *m/z* 393 (*M*⁺, 4 %), 364 (33), 223 (25), 209 (46), 149 (46), 57(74), and 36(100).

This compound was used without further purification in the next stage.

2-(2-Formamidoethyl)-1,4-dimethyl-6-phenylsulphonyloxyfluorene (132).

A mixture of acetic anhydride (2.5 cm³, 27.4 mmol) and 98 % formic acid (1 cm³, 28.7 mmol) was stirred at 55 °C, cooled and added to 2-(2-aminoethyl)-1,4-dimethyl-6-phenylsulphonyloxyfluorene (500 mg, 1.27 mmol). The mixture was stirred at 55 °C for 1.5 h, cooled, diluted with water and extracted with chloroform. The combined extracts were washed with water, saturated brine, dried (MgSO₄) and evaporated under reduced pressure to an orange gum. Chromatography on neutral alumina eluting with chloroform afforded the title compound as a colourless solid (441 mg, 82 %) m.p. 136.6 - 138 °C (Accurate mass, found: 421.1268. C₂₄H₂₃NO₄S requires: 421.1344.); λ_{max} (EtOH) 209 (ϵ 31 380 dm³ mol⁻¹ cm⁻¹), 265 infl, 272 (13 060), 288 (8 000), and 298 infl nm; ν_{max} (CHCl₃) 3445 (-NH), 1665 (-NHC=O), 1605, 1580 (ArC-C), 1365, and 1140 cm⁻¹(ArSO₂-OAr); δ_{H} (270 MHz, CDCl₃) 2.31 (3 H, s, Ar-CH₃), 2.38 (3 H, s, Ar-CH₃), 2.89 (2 H, t, J = 7 Hz, -CH₂CH₂NH), 3.52 (2 H, dt, J = 7 Hz and 7 Hz, -CH₂CH₂NH), 3.70 (2 H, s, 9-CH₂), 5.78 (1 H, brs, -CH₂NH), 6.92 (1 H, dd, J = 8 Hz and 2 Hz, 7-H), 6.92 (1 H, s, 3-H), 7.27 (1 H, d, J = 2 Hz, 5-H), 7.43 (1 H, d, J = 8 Hz, 8-H), 7.51 (2 H, t, J = 8 Hz, 2'- and 6'-H), 7.64 (1 H, t, J = 8 Hz, 4'-H), 7.84 (2 H, d, J = 8 Hz, 3'- and 5'-H), and 8.16 (1 H, s, -NCHO); m/z 421 (M^+ , 25 %), 376 (100), 363 (39), 235 (49), and 84 (67).

Attempted synthesis of 5,11-dimethyl-9-phenylsulphonyloxy-6H-pyrido [4,3-*b*] fluorene (133).

Method A.

Phosphorus pentoxide (40 mg, 0.28 mmol) was added, in two portions during 1 h, to a stirred solution of 2-(2-formamidoethyl)-1,4-dimethyl-6-phenylsulphonyloxyfluorene (47 mg, 0.11 mmol) in dry toluene (5 cm³) at 110 °C and the mixture heated, under an atmosphere of dry nitrogen, for 2 h. The cooled mixture was diluted with water, basified with solid sodium bicarbonate and extracted with chloroform. The combined extracts were washed with saturated brine, dried (Na₂SO₄) and evaporated

under reduced pressure to a brown oil. ^1H n.m.r. and i.r. spectroscopy showed this to be recovered starting material.

Method B.

A mixture of 2-(2-formamidoethyl)-1,4-dimethyl-6-phenylsulphonyloxy-fluorene (150 mg, 0.36 mmol) and freshly distilled phosphorus oxychloride (0.5 cm^3 , 0.54 mmol) in dry toluene (5 cm^3) was heated under reflux, under an atmosphere of dry nitrogen, for 2 h. Thin layer chromatography revealed the consumption of starting material and the cooled mixture was poured onto iced water, basified with 3 M sodium hydroxide and extracted with chloroform. The combined extracts were washed with water, saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to a black tar. Thin layer chromatographic analysis revealed this to be a multicomponent mixture.

Method C.

A mixture of 2-(2-formamidoethyl)-1,4-dimethyl-6-phenylsulphonyloxy-fluorene (87 mg, 0.21 mmol) and phosphorus pentachloride (100 mg, 0.53 mmol) in chloroform (5 cm^3) was stirred at room temperature for 16 h. Thin layer chromatography showed no change and the mixture was heated under reflux for 4 h. The cooled mixture was acidified with concentrated hydrochloric acid, stirred, basified with 3 M sodium hydroxide and extracted with chloroform. The combined extracts were washed with water, saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to a brown gum. Thin layer chromatographic analysis revealed this to be a multicomponent mixture.

Ethyl polyphosphate.

The reagent was prepared by heating phosphorus pentoxide (x g) with diethyl ether (x cm³) and chloroform (2 x cm³) under reflux until a clear solution was obtained (16 - 24 h).

Attempted synthesis of 5-11-dimethyl-9-phenylsulphonyloxy-6-*H*-pyrido[4,3-*b*]fluorene (133).

Method D.

A solution of 2-(2-formamidoethyl)-1,4-dimethyl-6-phenylsulphonyloxy-fluorene (170 mg, 0.4 mmol) in chloroform (7 cm³) was added to ethyl polyphosphate generated from 1 g of phosphorus pentoxide, and the mixture heated under reflux for 3 h. Thin layer chromatography showed that no change had occurred and the mixture was heated to 100 °C. The solvent was distilled from the mixture and the residue stirred at 100 °C for 1.5 h. The cooled mixture was diluted with water, basified with 3 M sodium hydroxide and extracted with chloroform. The combined extracts were washed with water, saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to an orange gum. ¹H n.m.r. and i.r. spectroscopy showed this to be recovered starting material.

Method E.

A solution of 2-(2-formamidoethyl)-1,4-dimethyl-6-phenylsulphonyloxy-fluorene (500 mg, 1.19 mmol) in chloroform (10 cm³) was added to ethyl polyphosphate, generated from 5 g phosphorus pentoxide, and the solvent removed by distillation. The residue was stirred at 180 °C for 1 h, cooled, diluted with water, basified with 3 M sodium hydroxide and extracted with chloroform. The combined extracts were washed with saturated brine, dried (Na₂SO₄) and evaporated under reduced pressure to a brown gum (130 mg). Thin layer chromatographic analysis

showed that the starting material had been consumed, but no new product was seen.

The same result was obtained by stirring at 150 °C for 1 h.

5,11-dimethyl-9-phenylsulphonyloxy-6H-pyrido[4,3-b]fluorene (133).

A solution of 2-(2-formamidoethyl)-1,4-dimethyl-6-phenylsulphonyloxy-fluorene (38 mg, 0.09 mmol) in chloroform (2 cm³) was added to ethyl polyphosphate, generated from 1 g phosphorus pentoxide, and the solvent removed by distillation. The residue was stirred at 120 °C for 1 h, cooled, diluted with water, basified with concentrated ammonia and extracted with ethyl acetate. The combined extracts were washed with water, dried (Na₂SO₄) and evaporated under reduced pressure to a red oil (40 mg), λ_{max} (EtOH) 252 sh, 260, 270 sh, and 293 inf nm; ν_{max} (CHCl₃) 1600, 1580 (ArC-C), 1370, and 1145 cm⁻¹ (ArSO₂-OAr).

The oil was dissolved in freshly distilled diglyme (5 cm³) and heated under reflux with 10 % palladium on carbon (10 mg), with dry nitrogen passed through the mixture, for 2.5 h. The cooled mixture was diluted with ethyl acetate, filtered through celite, washed with water, dried (Na₂SO₄) and evaporated under reduced pressure to a brown gum. Short path medium pressure chromatography eluting with triethylamine - ethyl acetate (2: 98) afforded the title compound as a yellow oil (8 mg, 22 %)

λ_{max} (EtOH) 260, 270, 279 sh, 296, 312, and 345 inf nm; ν_{max} (CHCl₃) 1605, 1580 (ArC-C), 1370, and 1145 cm⁻¹ (ArSO₂-OAr); δ_{H} (270 MHz, CDCl₃) 2.59 (3 H, s, Ar-CH₃), 2.77 (3 H, s, Ar-CH₃), 3.94 (2 H, s, 6-CH₂), 6.98 (1 H, dd, J = 8 Hz and 2 Hz, 8-H), 7.46 (1 H, d, J = 8 Hz, 7-H), 7.49 (1 H, s, 10-H), 7.49 (2 H, dd, J = 8 Hz and 8 Hz, 3'- and 5'-H), 7.64 (1 H, t, J = 8 Hz, 4'-H), 7.78 (1 H, d, J = 6 Hz, 4-H), 7.84 (2 H, d, J = 8 Hz, 2'- and 6'-H), 8.58 (1 H, d, J = 6 Hz, 3-H), and 9.62 (1 H, brs, 1-H); m/z 402 (M^+ , 74 %), 260 (100), 246 (21), and 217 (23).

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